

<b>2.04.106</b>	<b>Genetic Testing for CHARGE Syndrome</b>		
<b>Original Policy Date:</b>	October 31, 2014	<b>Effective Date:</b>	April 1, 2019
<b>Section:</b>	2.0 Medicine	<b>Page:</b>	Page 1 of 11

### Policy Statement

Genetic testing for CHARGE syndrome may be considered **medically necessary** to confirm a diagnosis in a patient with signs/symptoms of CHARGE syndrome when a definitive diagnosis cannot be made with clinical criteria(see Policy Guidelines section).

Genetic testing for CHARGE syndrome is considered **investigational** in all other situations.

### Policy Guidelines

A diagnosis of definitive CHARGE syndrome can be made clinically in individuals with all 4 major characteristics or 3 major and 3 minor characteristics (Lalani et al [2012]). In patients without the classical clinical criteria to diagnose CHARGE, in those with a milder phenotype, and/or in those with features that overlap with and cannot be distinguished from other syndromes, genetic testing may provide a definitive diagnosis.

Major characteristics include:

- Choanal atresia or stenosis
- Cranial nerve abnormality
- Ear anomalies/deafness
- Ocular coloboma

Minor characteristics include:

- Cardiac malformations
- Cleft lip and/or cleft palate
- Developmental delays
- Distinctive charge facial appearance, consisting of a prominent forehead and a prominent nasal bridge
- Genital hypoplasia
- Hypogonadotropic hypogonadism
- Short stature
- Tracheoesophageal fistula

Other, less frequent manifestations include:

- Attention-deficit/hyperactivity disorder
- Brain malformations
- Dental problems
- Immunodeficiency
- Kidney malformations
- Omphalocele
- Scoliosis
- Various behavioral problem
- Various limb abnormalities

This policy does not address preconception (carrier) testing and prenatal (in utero) testing.

### Genetics Nomenclature Update

The 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 evidence review updates starting in 2017 (see Table

PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUMAN Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to 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 PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

**Table PG1. 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 PG2. 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

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

### Coding

CPT code 81407 includes the following testing for CHARGE syndrome:

*CHD7* (chromodomain helicase DNA binding protein 7) (e.g., CHARGE syndrome), full gene sequence:

- **81407:** Molecular pathology procedure level 8

### Description

CHARGE syndrome is a rare genetic condition associated with multiple congenital anomalies. In many individuals, the diagnosis can be made based on clinical findings. However, the phenotype of the disease is highly variable, and some patients do not fulfill the criteria for a definitive diagnosis by clinical findings. Sequence analysis of the *CHD7* gene detects variants in most individuals with CHARGE syndrome.

### Related Policies

- N/A

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Genetic tests for CHARGE syndrome are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

## Rationale

### Background

#### CHARGE Syndrome

CHARGE syndrome is a rare genetic condition caused by variants of the *CHD7* gene on chromosome 8q12.1. The letters of CHARGE syndrome correspond to clinical features: C = ocular coloboma; H = heart defect; A = atresia choanae; R = retarded growth and development; G = genital hypoplasia; and E = ear anomalies/deafness. A number of other malformations are also common in this condition. In particular, hypoplasia of the semicircular canals has emerged as a frequent and distinctive CHARGE malformation.

Newborns with CHARGE syndrome typically have several major congenital malformations that affect vision, hearing, cardiovascular function, growth, development, neurologic function, and overall well-being. Mortality is relatively high in neonates with bilateral choanal atresia, cyanotic cardiac malformations, central nervous system malformations, and/or tracheoesophageal fistula. In a 1998 series, the death rate was 20% in the first month of life and about 50% by 6 months of age.<sup>1</sup> A formal 2005 epidemiologic study in Canada concluded that those who survived infancy were likely to have long-term survival.<sup>2</sup> Morbidity is chronic and multisystemic. Cognitive outcomes are difficult to assess because both motor skills and language do not necessarily reflect intellect in this group. About 75% have some degree of intellectual disability. Among the 25% with normal intelligence, many are well educated and live independently as adults.<sup>3</sup>

### Clinical Diagnosis

Investigators have debated extensively the relative importance of certain clinical signs. Consequently, the diagnostic criteria for CHARGE syndrome have been repeatedly revised. The complete phenotypic spectrum of CHARGE syndrome was only revealed after identification of the causative gene in 2004, and the phenotypic spectrum of the disease is highly variable. A 2012 review<sup>3</sup> proposed that the diagnosis of CHARGE syndrome be considered *definite* if an individual has 4 major characteristics or 3 major and 3 minor characteristics, criteria initially proposed by Blake (the Blake criteria),<sup>4</sup> and modified by Verloes.<sup>5</sup> Individuals with 1 or 2 major

characteristics and several minor characteristics would be considered to have *probable* or *possible* CHARGE syndrome (see Table 1).

**Table 1. Criteria for the Diagnosis of CHARGE Syndrome**

Characteristics	Prevalence
<b>Major</b>	
Ocular coloboma, which may be manifest in the iris and/or the retina, choroid, and optic disc, and sometimes as microphthalmia.	80%-90%
Choanal atresia or stenosis, which may be unilateral or bilateral. Complete bilateral choanal atresia is a life-threatening emergency in a newborn, because neonates are obligate nose breathers. Some CHARGE patients have a cleft palate, in which case the cleft fulfills this criterion.	50%-60%
CN abnormality, including hyposmia or anosmia (CN I), facial palsy (CN VII), auditory nerve hypoplasia causing sensorineural hearing loss (CN VIII), and/or swallowing problems with or without aspiration (CN IX and CN X).	70%-90%
Characteristic auditory manifestation of the external, middle, or inner ear. The external ear is often dysmorphic. A number of ossicular malformations of the middle ear are common. Sensorineural hearing loss is associated with a Mondini malformation of the cochlea, and vestibular dysfunction is caused by aplasia or hypoplasia of the semicircular canals in 95% of individuals with CHARGE. Temporal bone computed tomography is necessary to diagnose the cochlear and semicircular canal defects.	80%-100%
<b>Minor</b>	
Genital hypoplasia in boys is manifest as micropenis and cryptorchidism, and in girls as hypoplastic labia. Puberty may be delayed because of hypogonadotropic hypogonadism.	50%
Developmental delays, especially gross motor and language delays, which may be intrinsic qualities or caused by impaired balance, deafness, blindness, hypotonia, surgery, or other chronic illness.	100%
Congenital cardiac malformations.	80%
Short stature, often with postnatal onset.	75%
Cleft lip and/or cleft palate.	15%
Tracheoesophageal fistula.	15%
Distinctive CHARGE facial appearance, consisting of a prominent forehead and a prominent nasal bridge.	75%

CN: cranial nerve.

Other, less frequent manifestations include kidney malformations (25%), immunodeficiency, various limb abnormalities, scoliosis, dental problems, omphalocele, brain malformations, attention-deficit/hyperactivity disorder, and various behavioral problems.

The diagnosis of CHARGE syndrome is primarily clinical, based on use of the diagnostic criteria above.

External ear anomalies, abnormalities of cranial nerve function, semicircular canal hypoplasia, and gross motor delays seem to be consistent phenotypic manifestations in CHARGE syndrome, but fully one-third of CHARGE patients will lack choanal atresia and/or ocular coloboma, with the most mildly affected showing only abnormal ears and a balance disturbance. Consequently, CHARGE syndrome can closely resemble several other genetic and teratogenic conditions, such as the 22q11.2 deletion syndrome, Kallmann syndrome, VACTERL association, Kabuki syndrome, renal coloboma syndrome, cat-eye syndrome, Joubert syndrome, branchio-oto-renal syndrome, and retinoic embryopathy. In 1 patient with velo-cardio-facial syndrome in whom the chromosome 22q11.2 microdeletion was ruled out, a *CHD7* variant was documented.<sup>6</sup> Several patients with Kallmann syndrome were found to have *CHD7* disease-associated variants.

In recognition of this expanding CHARGE phenotype, Bergman et al (2011) proposed a revision of cardinal and supporting features, and suggested that *CHD7* testing be offered to individuals on the milder end of the phenotypic spectrum.<sup>7</sup> Their algorithmic approach to diagnosis also

incorporated temporal bone computed tomography scans as an important but not necessary component of the diagnostic workup. Although CHARGE syndrome is most often related to a sporadic disease-associated variant, some investigators (2014) have proposed that family history (any first-degree relative with at least 1 major feature of CHARGE) be incorporated into the clinical diagnosis of CHARGE syndrome as a major diagnostic criterion.<sup>8</sup>

### **Genetic Etiology**

In 2014, certain variants of the *CHD7* gene, which encodes chromodomain helicase DNA binding protein, were found to cause CHARGE syndrome. In mouse models, the *CHD7* gene has been associated with neural crest migration.<sup>9</sup> Almost all pathogenic variants have proven to be single nucleotide variants, though on rare occasions there may be a chromosomal translocation with a breakpoint within the *CHD7* gene. Microdeletions, as would be detected with chromosome microarray analysis, are rare and probably occur in no more than 2% of individuals.

Most instances of CHARGE syndrome are sporadic events in a family and appear to be caused by de novo *CHD7* disease-associated variants. On rare occasions, CHARGE can be inherited as an autosomal dominant condition. Individuals with CHARGE who reproduce have a 50% chance of transmitting the variant to their offspring. Recurrence in siblings because of germline mosaicism has also been reported. The prevalence of CHARGE syndrome is estimated at 1 in 8500 live births.<sup>2</sup>

Genetic testing for variants of *CHD7* is available from several commercial laboratories and is generally performed through Sanger sequence analysis. If no disease-associated variant is identified by Sanger sequencing, deletion and duplication analysis can be performed to identify large deletions.

### **Treatment**

Extensive management guidelines have been developed for CHARGE syndrome.<sup>4,7,10</sup> They include periodic examinations and treatment by ophthalmology, otolaryngology, audiology, occupational therapy, speech therapy, gastroenterology, endocrinology, cardiology, neurology, developmental pediatrics, and genetics. Routine investigations would include choanal computed tomography, nasal endoscopy, brainstem auditory-evoked responses, temporal bone computed tomography, swallowing studies, renal ultrasound, gonadotropin testing, echocardiography, brain magnetic resonance imaging, growth hormone testing, and genetic counseling. Immunologic assessment should be considered, particularly if patients have recurrent lung or ear infections.<sup>11</sup> Based on their evaluation of immune dysfunction in children with CHARGE syndrome, Wong et al (2015) recommended immunologic evaluation of patients with CHARGE syndrome who have recurrent infections.<sup>12</sup> Many of these resources might be provided in due course for a child with multiple congenital anomalies in the absence of an exact etiologic diagnosis. However, a number of specific investigations and therapies might not be considered unless CHARGE syndrome has been definitively diagnosed on a clinical basis or, for mildly affected individuals, as the result of genetic testing.

### **Literature Review**

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

## Testing for suspected CHARGE Syndrome

### Clinical Context and Test Purpose

In many cases, the individual clinical manifestations of CHARGE syndrome would present on their own and require management without a diagnosis of the larger syndrome. However, given the multisystemic nature of the disease and the well-established recommendations for surveillance for early complications, it is highly likely that outcomes are improved for individuals with CHARGE syndrome if a diagnosis is made.

The purpose of genetic testing for *CHD7* in patients who have suspected CHARGE syndrome is to inform a decision whether to pursue additional management steps for CHARGE.

The questions addressed in this evidence review are: (1) Is there evidence that testing for disease-associated variants in *CHD7* has clinical validity?; and (2) Does patient management change in a way that potentially improves outcomes as a result of testing?

The following PICOTS were used to select literature to inform this review.

### Patients

The population of interest includes patients with signs and/or symptoms of CHARGE syndrome, but who do not meet the clinical definition of CHARGE syndrome.

### Interventions

Most disease-causing variants in *CHD7* associated with CHARGE syndrome are single nucleotide variants (SNVs); therefore, Sanger sequencing is an appropriate first step in testing. If that testing is negative, deletion/duplication analysis of the *CHD7* gene could be obtained.

### Comparators

The comparator of interest is standard clinical care without genetic testing, where decisions about medical therapy or evaluations are based on symptoms at the time of presentation.

### Timing

Trials of genetic testing or treatment strategies in this population were not found. Morbidity and mortality over the course of several years given the disease presentation in early childhood would be reasonable.

### Setting

CHARGE syndrome is likely managed at least in part by subspecialists. Depending on the acuity of the initial presentation, the patient may be an inpatient or an outpatient. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

### Simplifying Test Terms

There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of

detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

### Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

### Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The yield of genetic testing in individuals with either diagnosed or suspected CHARGE syndrome can vary depending on factors such as age or family history, and may depend on the clinical criteria used. As reported in the Clinical Utility Gene Card (2015), in over 90% of the patients who fulfill the Blake or Verloes criteria, a disease-associated variant is found.<sup>13</sup>

In those with suspected CHARGE syndrome, a disease-associated variant is found in 30% to 60% of patients.<sup>13</sup> The proportion varies in individual studies, especially those with small sample sizes. For example, Lalani et al (2006) conducted genetic testing in 110 individuals with a clinical diagnosis of CHARGE syndrome and found disease-associated variants in *CHD7* in 64 (58%) of study participants.<sup>14</sup> A study by Vuorela et al (2007) tested 74 patients with suspected CHARGE syndrome and found disease-associated variants in 30 (41%) of them.<sup>15</sup>

CHARGE syndrome sometimes can be excluded if a patient does not fulfill the clinical criteria and does not carry a disease-associated variant or deletion of *CHD7*. Some conditions that mimic CHARGE syndrome are 22q11 deletion syndrome, VACTERL association, chromosomal disorders (e.g., deletions 3p12p21.2), disorders caused by teratogens (e.g., maternal diabetes, isotretinoin [Accutane]), and Kallmann syndrome.<sup>10</sup>

The clinical specificity (proportion of patients who do not have the disease who have a negative test) can vary depending on factors such as age or family history. The clinical variability of CHARGE syndrome is considerable. If the diagnosis is based on the Blake criteria, some individuals with CHARGE will be missed. The clinical specificity is greater than 95%, because less than 5% of the patients with a *CHD7* disease-associated variant do not completely fulfill these criteria. However, it should be taken into account that the mild end of the phenotypic spectrum is not yet completely known.<sup>10</sup>

The penetrance is high, estimated to be 100%, but there is high clinical variability.<sup>13</sup>

The negative predictive value (probability of not developing the disease if the test is negative), assuming an increased risk based on family history, is 100% if the index case in the family has been tested. If the index case in the family has not been tested, it depends on the a priori chance that the index will be found to have a disease-associated variant, which is 60% to 90%.

There are no known genotype-phenotype correlations for specific *CHD7* variants and CHARGE syndrome manifestations; therefore, the phenotype cannot be predicted from the genotype. For example, a study by Jongmans et al (2006) of 107 patients tested for *CHD7* variants did not identify any obvious genotype-phenotype correlations.<sup>16</sup>

**Section Summary: Clinically Valid**

Studies of the testing yield for *CHD7* variants have suggested that, in individuals with suspected CHARGE syndrome, approximately 30% to 60% will have an identified *CHD7* variant. There is high clinical specificity. Genetic testing for CHARGE syndrome is very good for confirming a diagnosis, but a negative test does not rule out the disease.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Most cases of CHARGE syndrome can be diagnosed clinically using established major and minor criteria (see Table 1). Scanning of the temporal bones often elicits abnormalities in the semicircular canals, which brings more specificity to the diagnosis. However, not all patients fulfill the clinical criteria for CHARGE syndrome and, based on clinical findings, may be considered to have possible or probable CHARGE syndrome. Mildly affected patients may only have one or a few of the features of CHARGE syndrome. Overlapping features with other syndromes may also make a clinical diagnosis challenging. Genetic testing may be useful in patients who do not have the classical CHARGE characteristics and who may be at risk for the long-term complications of CHARGE syndrome.<sup>10</sup>

While extensive management guidelines have been developed for CHARGE syndrome (see Background section),<sup>3</sup> no randomized controlled trials were identified.

**Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

A chain of evidence can be developed based on the clinical validity. In individuals with suspected but not confirmed CHARGE syndrome, for whom genetic testing confirms a diagnosis, a definitive diagnosis will likely direct patient care according to established clinical management guidelines for CHARGE syndrome, including referrals to the proper specialists, treatment of manifestations, prevention of secondary complications, and surveillance.

**Section Summary: Clinically Useful**

Most cases of CHARGE syndrome can be diagnosed through established clinical criteria. However, patients who do not meet clinical criteria due to variability in clinical presentation are likely to benefit from genetic testing for CHARGE syndrome. A definitive genetic diagnosis of CHARGE would direct patient care to established clinical management guidelines for CHARGE syndrome.

**Summary of Evidence**

For individuals who have signs and/or symptoms of CHARGE syndrome who receive genetic testing for variants in the *CHD7* gene, the evidence includes case series. Relevant outcomes are overall survival, test accuracy and validity, symptoms, morbid events, functional outcomes, quality of life, and resource utilization. Although the clinical sensitivity of testing *CHD7* variant testing cannot be specifically defined, over 90% of patients who fulfill the Blake or Verloes criteria for CHARGE syndrome have a *CHD7* variant. A definitive diagnosis may end the need for additional testing in the etiologic workup and direct patient care according to established clinical management guidelines for CHARGE syndrome, including referrals to appropriate

specialists, treatment of manifestations, prevention of secondary complications, and surveillance. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

### Supplemental Information

#### Practice Guidelines and Position Statements

Bergman et al (2011) proposed guidelines for *CHD7* analysis and stated that, while the diagnosis of CHARGE syndrome remains primarily a clinical diagnosis (see Table 1), molecular testing can confirm the diagnosis in mildly affected patients.<sup>7</sup>

#### U.S. Preventive Services Task Force Recommendations

Not applicable.

#### Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

#### Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in January 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

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### Documentation for Clinical Review

**Please provide the following documentation (if/when requested):**

- History and physical and/or consultation notes including:
  - Family history
  - How test result will impact clinical decision making
  - Reason for performing test
  - Signs/symptoms/test results related to reason for genetic testing
- Lab results documenting carrier status or genetic disorder
- Physician order for genetic test
- Name and description of genetic test
- CPT codes billed for the particular genetic test

### Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.*

#### MN/IE

**The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.**

Type	Code	Description
CPT®	81407	Molecular Pathology Procedure Level 8
HCPCS	None	
ICD-10 Procedure	None	

### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
10/31/2014	BCBSA Medical Policy adoption	Medical Policy Committee
01/01/2017	Policy revision without position change	Medical Policy Committee
04/01/2017	Policy revision without position change	Medical Policy Committee
04/01/2018	Policy revision without position change	Medical Policy Committee
04/01/2019	Policy revision without position change	Medical Policy Committee

## Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*