Genetic Testing for CHARGE Syndrome

Policy # 00393
Original Effective Date: 11/20/2013
Current Effective Date: 11/21/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing for CHARGE syndrome to confirm a diagnosis in a patient with signs/symptoms of CHARGE syndrome when a definitive diagnosis cannot be made with clinical criteria to be **eligible for coverage** *(See Note below).*

Note:
A diagnosis of definite CHARGE syndrome can be made clinically in individuals with all 4 major characteristics or 3 major and 3 minor characteristics. 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 ocular coloboma, choanal atresia or stenosis, cranial nerve (CN) abnormality, ear anomalies/deafness.

Minor Characteristics include genital hypoplasia, hypogonadotrophic hypogonadism, developmental delays, cardiac malformations, short stature, cleft lip and/or cleft palate, tracheoesophageal fistula, distinctive CHARGE facial appearance, consisting of a prominent forehead and a prominent nasal bridge. Other, less frequent manifestations include kidney malformations, immunodeficiency, various limb abnormalities, scoliosis, dental problems, omphalocele, brain malformations, attention deficit hyperactivity disorder (ADHD), and various behavioral problems.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for CHARGE syndrome in all other situations to be **investigational.***

Background/Overview

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. A formal 2005 epidemiologic study in Canada concluded that those who survived infancy were likely to have long-term survival. 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.

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 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), and modified by Verloes. 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
Major		
	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%

Characteristics		Prevalence
Minor		
	Genital hypoplasia in boys is manifest as micropenis and cryptorchidism, and in girls as hypoplasic 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. 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. 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.

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. 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.

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. 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. 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. 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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.

Centers for Medicare and Medicaid Services (CMS)
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.

Rationale/Source

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, and
- 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.

In those with suspected CHARGE syndrome, a disease-associated variant is found in 30% to 60% of patients. 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. A study by Vuorela et al (2007) tested 74 patients with suspected CHARGE syndrome and found disease-associated variants in 30 (41%) of them.

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 (eg, deletions 3p12p21.2), disorders caused by teratogens (eg, maternal diabetes, isotretinoin [Accutane]), and Kallmann syndrome.

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.

The penetrance is high, estimated to be 100%, but there is high clinical variability.
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.

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.

While extensive management guidelines have been developed for CHARGE syndrome (see Background section), 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.

Genetic Testing for CHARGE Syndrome

Policy # 00393
Original Effective Date: 11/20/2013
Current Effective Date: 11/21/2018

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.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Genetic Testing for CHARGE Syndrome", 2.04.106, 2:2018.
2. Tellier AL, Cormier-Daire V, Abadie V, et al. CHARGE syndrome: report of 47 cases and review. *Am J Med Genet.* Apr 13 1998;76(5):402-409. PMID 9556299
3. Issekutz KA, Graham JM, Jr., Prasad C, et al. An epidemiological analysis of CHARGE syndrome: preliminary results from a Canadian study. *Am J Med Genet A.* Mar 15 2005;133A(3):309-317. PMID 15637722
4. Lalani SR, Hefner MA, Belmont JW, et al. CHARGE Syndrome. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews*. Seattle, WA: University of Washington; 2012.
5. Blake KD, Davenport SL, Hall BD, et al. CHARGE association: an update and review for the primary pediatrician. *Clin Pediatr (Phila).* Mar 1998;37(3):159-173. PMID 9545604
6. Verloes A. Updated diagnostic criteria for CHARGE syndrome: a proposal. *Am J Med Genet A.* Mar 15 2005;133A(3):306-308. PMID 15666308
7. Jain S, Kim HG, Lacbawan F, et al. Unique phenotype in a patient with CHARGE syndrome. *Int J Pediatr Endocrinol.* Oct 13 2011;2011:11. PMID 21995344
8. Bergman JE, Janssen N, Hoefsloot LH, et al. CHD7 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype. *J Med Genet.* May 2011;48(5):334-342. PMID 21378379
9. Hughes SS, Welsh HI, Safina NP, et al. Family history and clefting as major criteria for CHARGE syndrome. *Am J Med Genet A.* Jan 2014;164A(1):48-53. PMID 24214489
10. Schulz Y, Wehner P, Opitz L, et al. CHD7, the gene mutated in CHARGE syndrome, regulates genes involved in neural crest cell guidance. *Hum Genet.* Aug 2014;133(8):997-1009. PMID 24728844
11. Blake K, van Ravenswaaij-Arts CM, Hoefsloot L, et al. Clinical utility gene card for: CHARGE syndrome. *Eur J Hum Genet.* Sep 2011;19(9). PMID 21407266
12. Hsu P, Ma A, Wilson M, et al. CHARGE syndrome: a review. *J Paediatr Child Health.* Jul 2014;50(7):504-511. PMID 24548020
13. Wong MT, Lambeck AJ, van der Burg M, et al. Immune dysfunction in children with CHARGE syndrome: a cross-sectional study. *PLoS One.* Nov 2015;10(11):e0142350. PMID 26544072
14. van Ravenswaaij-Arts CM, Blake K, Hoefsloot L, et al. Clinical Utility Gene Card for: CHARGE syndrome - update 2015. *Eur J Hum Genet.* Nov 2015;23(11). PMID 25689928
15. Lalani SR, Safiullah AM, Fernbach SD, et al. Spectrum of CHD7 mutations in 110 individuals with CHARGE syndrome and genotype-phenotype correlation. *Am J Hum Genet.* Feb 2006;78(2):303-314. PMID 16400610
16. Vuorela P, Ala-Mello S, Saloranta C, et al. Molecular analysis of the CHD7 gene in CHARGE syndrome: identification of 22 novel mutations and evidence for a low contribution of large CHD7 deletions. *Genet Med.* Oct 2007;9(10):690-694. PMID 18073582
17. Jongmans MC, Admiraal RJ, van der Donk KP, et al. CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene. *J Med Genet.* Apr 2006;43(4):306-314. PMID 16155193

Genetic Testing for CHARGE Syndrome

Policy # 00393
Original Effective Date: 11/20/2013
Current Effective Date: 11/21/2018

Policy History

Original Effective Date: 11/20/2013
Current Effective Date: 11/21/2018
11/07/2013 Medical Policy Committee review
11/20/2013 Medical Policy Implementation Committee approval. New policy.
11/06/2014 Medical Policy Committee review
11/21/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015 Medical Policy Committee review
11/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged
11/03/2016 Medical Policy Committee review
11/16/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017 Medical Policy Committee review
11/15/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged
11/08/2018 Medical Policy Committee review
11/21/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 11/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81407
HCPCS	No codes
ICD-10 Diagnosis	E78.71-E78.72, Q87.2-Q87.89, Q89.8

Genetic Testing for CHARGE Syndrome

Policy # 00393
Original Effective Date: 11/20/2013
Current Effective Date: 11/21/2018

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.