Genetic Testing for CHARGE Syndrome

Policy # 00393
Original Effective Date: 11/20/2013
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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 mutation testing for CHARGE syndrome in all other situations to be investigational.*

Background/Overview
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 definite diagnosis by clinical findings. Sequence analysis of the chromodomain helicase deoxyribonucleic acid (DNA) binding protein 7 (CHD7) coding region detects mutations in most individuals with CHARGE syndrome.
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Description of the Disease
CHARGE syndrome is a rare genetic condition caused by mutations 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. However, a number of other malformations are also common in this condition. In particular, hypoplasia of the semi-circular 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 (CNS) malformations, and/or tracheoesophageal fistula. In one series, the death rate was 20% in the first month of life and about 50% by 6 months of age. A formal epidemiologic study in Canada concluded that those who survived infancy were likely to have long-term survival. Morbidity is chronic and multi-systemic. Cognitive outcome is 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.

In addition, investigators have conducted an extended debate about the relative importance of certain clinical signs. Consequently, the diagnostic criteria for CHARGE syndrome have been repeatedly revised.

Clinical Diagnosis of CHARGE Syndrome
The complete phenotypic spectrum of CHARGE was only revealed after identification of the causative gene in 2004, and the phenotypic spectrum of the disease is highly variable.

A 2012 review proposes 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.

Major Characteristics
Ocular coloboma, which may be manifest in the iris and/or the retina, choroid, and optic disc, and sometimes as microphthalmia. [Present in 80-90% of affected individuals]

Choanal atresia or stenosis, which may be unilateral or bilateral. Complete bilateral choanal atresia is a life-threatening emergency in a newborn, since neonates are obligate nose breathers. Some CHARGE patients have a cleft palate, in which case the cleft fulfills this criterion. [50-60%]

Cranial nerve abnormality, including hyposmia or anosmia (CN I), facial palsy (CN VII), auditory nerve hypoplasia causing sensorineural hearing loss (CN VIII), and/or swallowing problems [70-90%] with or without aspiration (CN IX and CN X).
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Characteristic auditory manifestation of the external, middle, or inner ear. [80-100%] 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 (CT) is necessary to diagnose the cochlear and semicircular canal defects.

Minor Characteristics
Genital hypoplasia in boys is manifest as micropenis and cryptorchidism, and in girls as hypoplastic labia.

Puberty may be delayed because of hypogonadotrophic 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%]

Other, less frequent manifestations include kidney malformations [25%], immunodeficiency, various limb abnormalities, scoliosis, dental problems, omphalocele, brain malformations, ADHD, and various behavioral problems.

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

External ear anomalies, abnormalities of CN 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 colobomata, 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, Branchiootorenal syndrome, and retinoic embryopathy. In one patient with velo-cardio-facial syndrome in whom the chromosome 22q11.2 microdeletion was ruled out, a CHD7 mutation was documented. Several patients with Kallmann syndrome were found to have CHD7 mutations.

In recognition of this expanding CHARGE phenotype, Bergman et al. have proposed a revision of cardinal and supporting features and suggest that CHD7 testing be offered to individuals on the milder end of the
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phenotypic spectrum. Their algorithmic approach to diagnosis also incorporates temporal bone CT scans as an important but not invariably necessary component of the diagnostic workup.

Genetics of CHARGE syndrome
In 2004, mutations of *CHD7*, which encodes chromodomain helicase DNA-binding protein, were found to cause CHARGE syndrome. Almost all pathogenic mutations have proven to be point mutations, 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 testing, 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* mutations, but on rare occasions CHARGE can be inherited as an autosomal dominant condition. Recurrence in siblings because of germline mosaicism has also been reported. The prevalence of CHARGE syndrome is estimated at 1 in 8,500 live births.

Treatment of CHARGE syndrome
Extensive management guidelines have been developed for CHARGE syndrome. These 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 CT, nasal endoscopy, brainstem auditory evoked responses, temporal bone CT, swallowing studies, renal ultrasound, gonadotropin testing, echocardiography, brain magnetic resonance imaging (MRI), growth hormone testing, and genetic counseling. 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 was definitively diagnosed on a clinical basis, or, for mildly affected individuals, as the result of genetic testing.

Genetic testing for mutations of *CHD7* is commercially available from several commercial laboratories.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
No U.S. FDA-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

Centers for Medicare and Medicaid Services (CMS)
No national coverage determination is identified.

Rationale/Source
Literature that describes the analytic validity, clinical validity, and clinical utility of testing for CHARGE syndrome was sought.
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Analytic Validity (technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent)

Almost all pathogenic mutations are point mutations. On rare occasions, there may be a chromosomal translocation with a break point within the CDH7 gene. Microdeletions or whole-exon deletions occur in less than 5% of patients.

Sequencing of the CHD7 gene has high analytical sensitivity and specificity. Sequence analysis detects greater than 99% of the (point) mutations present in the area that has been investigated. Testing that identifies deletions not readily detected by sequence analysis includes multiplex ligation-dependent probe amplification (MLPA) or chromosomal microarray analysis. Multiplex ligation-dependent probe amplification has an estimated sensitivity of greater than 95% for deletions and greater than 90% for individual exons.

The analytical sensitivity (proportion of positive tests if the genotype is present) depends on the method used. If only CHD7 sequencing is performed, deletions are missed less than 5% of the time due to whole-exon or whole-gene deletions. If sequencing is combined with MLPA, it is 100%.

The analytical specificity (proportion of negative tests if the genotype is not present) is almost 100% (some variants may erroneously be interpreted as pathogenic).

Clinical Validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease)

Clinical sensitivity and specificity are also high.

The clinical sensitivity (proportion of positive tests if the disease is present) can be dependent on variable factors such as age or family history, and may depend on the clinical criteria used. In over 95% of the patients who fulfill the Blake or Verloes criteria, a mutation is found. In those with suspected CHARGE syndrome, a mutation is found in 60–70% of patients.

CHARGE syndrome sometimes can be excluded if a patient does not fulfill the clinical criteria and does not carry a mutation or deletion of CHD7. Some conditions that mimic CHARGE syndrome are 22q11 deletion syndrome, VACTERL (vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities) association, chromosomal disorders (e.g., deletions 3p12p21.2) disorders caused by teratogens (e.g., maternal diabetes, Accutane), and Kallmann syndrome.

The clinical specificity (proportion of negative tests if the disease is not present) can be dependent on variable 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%, since less than 5% of the patients with a CHD7 mutation do not completely fulfill these criteria. However, it should be taken into account that the mild end of the phenotypic spectrum is not completely known yet.
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Therefore, genetic testing for CHARGE syndrome is very good for confirming a diagnosis, but a negative test does not rule out the disease.

The positive clinical predictive value (life-time risk to develop the disease if the test is positive) is 100%, but there is high clinical variability.

The negative clinical 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 of the index to find a mutation, which is 60-90%.

There are no known genotype-phenotype correlations for specific CHD7 mutations and CHARGE syndrome manifestations, and therefore, the phenotype cannot be predicted from the genotype.

Clinical Utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes)

Individual
Most cases of CHARGE syndrome can be diagnosed clinically using established major and minor criteria. Scanning of the temporal bones often elicits abnormalities in the semi-circular 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 may be at risk for the long-term complications of CHARGE syndrome.

Extensive management guidelines have been developed for CHARGE syndrome. These 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 CT, nasal endoscopy, brainstem auditory evoked responses, temporal bone CT, swallowing studies, renal ultrasound, gonadotropin testing, echocardiography, brain MRI, growth hormone testing, and genetic counseling.

Relatives
Almost all patients diagnosed with CHARGE syndrome do not have an affected parent as most are de novo mutations. Only rare instances of transmission from a mildly affected parent have been reported. Therefore, genetic testing in relatives of a patient with CHARGE syndrome has low clinical utility.
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Preconception (carrier) testing and prenatal (in utero) testing can also be performed, but are not addressed in this literature review.

Summary

CHARGE syndrome is a rare genetic syndrome with multiple associated malformations. Established clinical criteria can provide a diagnosis of definite CHARGE syndrome in some patients; however, due to the variable phenotypes associated with CHARGE syndrome, some patients may be categorized clinically as having possible or probable CHARGE syndrome.

CDH7 is the only gene currently known to be associated with CHARGE syndrome. The analytic sensitivity and specificity for detecting mutations in the CHD7 gene is high. The clinical sensitivity and specificity are also high: among patients with a clinical diagnosis of definite CHARGE syndrome, 90-95% have a mutation of CHD7. For individuals with possible or probable CHARGE syndrome, CHD7 analysis is positive for a mutation in 65-70% of cases.

The clinical utility of making a definite diagnosis of CHARGE syndrome is high, in that confirming a diagnosis in a patient will lead to changes in clinical management, including clinical assessment and treatment recommendations that are well-defined. The clinical utility of genetic testing for CHARGE syndrome is for patients in whom a definite diagnosis cannot be made clinically. Therefore, 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.

Almost all cases of CHARGE syndrome are a result of a de novo mutation, and therefore testing of relatives of a patient with CHARGE syndrome has low clinical utility. Therefore, mutation testing for CHARGE syndrome is considered investigational in all other situations.

References

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Next Scheduled Review Date:  11/2014

*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
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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.

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