Medical Policy
Genetic Testing for CHARGE Syndrome

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Policy Number: 540
BCBSA Reference Number: 2.04.106

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

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.

Mutation testing for CHARGE syndrome is INVESTIGATIONAL in all other situations.

Prior Authorization Information
Commercial Members: Managed Care (HMO and POS)
Prior Authorization is NOT required.

Commercial Members: PPO, and Indemnity
Prior Authorization is NOT required.

Medicare Members: HMO BlueSM
Prior Authorization is NOT required.

Medicare Members: PPO BlueSM
Prior Authorization is NOT required.

CPT Codes / HCPCS Codes / ICD-9 Codes
The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s
Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

### CPT Codes

<table>
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<th>CPT codes:</th>
<th>Code Description</th>
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<tr>
<td>81407</td>
<td>Molecular pathology procedure, Level 8 (eg, analysis of (26-50) exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of (&gt;50) exons, sequence analysis of multiple genes on one platform)</td>
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### 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 definite diagnosis by clinical findings. Sequence analysis of the chromodomain helicase DNA binding protein 7 (CHD7) coding region detects mutations in most individuals with CHARGE syndrome.

### Background

**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. (1) A formal epidemiologic study in Canada concluded that those who survived infancy were likely to have long-term survival. (2) 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. (3) (4)

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 (3) 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), (5) and modified by Verloes. (6) 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).

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, omphalocle, brain malformations, attention deficit hyperactivity disorder (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 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 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
phenotypic spectrum. (4) 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. (2)

Treatment of CHARGE syndrome
Extensive management guidelines have been developed for CHARGE syndrome. (3-5, 7) 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.

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.
**Policy History**

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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**