Medical Policy
Genetic Testing for CHARGE Syndrome

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Policy Number: 540
BCBSA Reference Number: 2.04.106
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
None

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

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.

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

A diagnosis of definite CHARGE syndrome can be made clinically in individuals with all 4 major characteristics or 3 major and 3 minor characteristics (Lalani, 1993; updated 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 ocular coloboma, choanal atresia or stenosis, cranial nerve abnormality, ear anomalies/deafness.

Minor characteristics include genital hypoplasia, hypogonadotropic hypogonadism, developmental delays, cardiac malformations, short stature, cleft lip and/or cleft palate, tracheoesophageal fistula, and 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, and various behavioral problems.

This policy does not address preconception (carrier) testing and prenatal (in utero) testing.
Medicare HMO Blue\textsuperscript{SM} and Medicare PPO Blue\textsuperscript{SM} Members

This is not a covered service.

\textbf{Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)}

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

\textbf{Prior Authorization Information}

Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required. Yes indicates that prior authorization is required. No indicates that prior authorization is not required. N/A indicates that this service is primarily performed in an inpatient setting.

| Outpatient |
|-----------------|-------------|
| Commercial Managed Care (HMO and POS) | No |
| Commercial PPO and Indemnity | No |
| Medicare HMO Blue\textsuperscript{SM} | This is not a covered service. |
| Medicare PPO Blue\textsuperscript{SM} | This is not a covered service. |

\textbf{CPT Codes / HCPCS Codes / ICD Codes}

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

\textbf{CPT Codes}

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
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<tbody>
<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>
</tr>
</tbody>
</table>

\textbf{Description}

\textbf{CHARGE SYNDROME}

CHARGE syndrome is a rare genetic condition caused by variants of the \textit{CHD7} gene on chromosome 8q12.\textsuperscript{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.\textsuperscript{1}
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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td><strong>Major</strong></td>
<td></td>
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<tr>
<td>Ocular coloboma, which may be manifest in the iris and/or the retina, choroid, and optic disc, and sometimes as microphthalmia.</td>
<td>80%-90%</td>
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<tr>
<td>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.</td>
<td>50%-60%</td>
</tr>
<tr>
<td>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).</td>
<td>0%-90%</td>
</tr>
<tr>
<td>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.</td>
<td>80%-100%</td>
</tr>
<tr>
<td>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.</td>
<td></td>
</tr>
<tr>
<td><strong>Minor</strong></td>
<td></td>
</tr>
<tr>
<td>Genital hypoplasia in boys is manifest as micropenis and cryptorchidism, and in girls as hypoplastic labia. Puberty may be delayed because of hypogonadotropic hypogonadism.</td>
<td>50%</td>
</tr>
<tr>
<td>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.</td>
<td>100%</td>
</tr>
<tr>
<td>Congenital cardiac malformations.</td>
<td>80%</td>
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<tr>
<td>Short stature, often with postnatal onset.</td>
<td>75%</td>
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<tr>
<td>Cleft lip and/or cleft palate.</td>
<td>15%</td>
</tr>
<tr>
<td>Tracheoesophageal fistula.</td>
<td>15%</td>
</tr>
<tr>
<td>Distinctive CHARGE facial appearance, consisting of a prominent forehead and a prominent nasal bridge.</td>
<td>75%</td>
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</tbody>
</table>

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 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 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) have 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 (CT) scans as an important but not invariantly 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 CHD7, which encodes chromodomain helicase DNA-binding protein, were found to cause CHARGE syndrome. In mouse models, the CHD7 gene has been found to be 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 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 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/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.

**Summary**
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 CHD7 gene detects variants in most individuals with CHARGE syndrome.

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. The analytic sensitivity and specificity for detecting disease-associated variants in the CHD7 gene are high. 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.

### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>4/2017</td>
<td>BCBSA National medical policy review. Policy clarified. “Mutation testing” changed to “genetic testing” in investigational policy statement. 4/1/2017</td>
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<tr>
<td>2/2017</td>
<td>Non-coverage for Medicare Advantage members clarified based on Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000). 2/1/2017</td>
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<tr>
<td>7/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
</tr>
<tr>
<td>10/2014</td>
<td>New references added from BCBSA National medical policy.</td>
</tr>
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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