

POLICY TITLE	GENETIC TESTING FOR CHARGE SYNDROME
POLICY NUMBER	MP 2.322

Clinical Benefit	 MINIMIZE SAFETY RISK OR CONCERN. MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. Assure appropriate level of care. Assure appropriate duration of service for interventions. Assure that recommended medical prerequisites have been met. 	
	□ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.	
Effective Date:	7/1/2025	

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I. POLICY

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

Genetic testing for CHARGE syndrome is considered **investigational** in all other situations. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

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 individuals 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, 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.

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



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GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society 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 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.

Previous	Updated	Definition	
Mutation	Diseased-associated Variant	Disease-associated change in the DNA sequence.	
	Variant	Change in DNA sequence	
	Familial Variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first- degree relatives.	

Table PG1. Nomenclature to Report on Variants Found in DNA

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	Change in DNA sequence with uncertain effects on disease
significance	
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association of Molecular Pathology.

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing.



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Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

II. PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-managementguidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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 individuals 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.

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 = 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. For example, 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 (CNS) 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 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. Morbidity can be reduced by early diagnosis and treatment.

Clinical Diagnosis

Investigators have debated extensively the relative importance of certain clinical signs. Consequently, the diagnostic criteria for CHARGE syndrome have been repeatedly revised.

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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 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.

Table 1. Criteria for the Diagnosis of CHARGE Syndrome

Characteris	tics	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%
Minor		
	Genital hypoplasia in boys manifests 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%



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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. A systematic review and meta-analysis by Thomas et al (2022) investigated the prevalence of phenotypic characteristics and variability in CHARGE syndrome. Prevalence estimates were highest for developmental delay (84%), intellectual disability (64%), aggressive behavior (48%), sleep difficulties (45%), and self-injurious behavior (44%). Meta-regression indicated significant associations between intellectual disability and choanal atresia or inner ear anomalies, and sleep difficulties and growth deficiency or gross motor difficulties.

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 velocardio-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.



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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.

CHARGE syndrome does not have sex-linked expression and hence affects males and females equally. 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

Management (medical or surgical) is based on presentation timing, features, and severity. 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 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.

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 (CLIA). Genetic tests for CHARGE syndrome are



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available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIAs for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

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.

V. DEFINITIONS

N/A

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations are based on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

Capital Blue Cross' medical policies are developed to assist in administering a member's benefits. These medical policies do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

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VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedu	re Codes				
81407					

ICD-10-CM Diagnosis Code	Description
Q99.8	Other specified congenital anomalies (includes CHARGE syndrome)

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X. POLICY HISTORY

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MP 2.322	06/04/2020 Consensus Review. No change to policy statements. Coding
	reviewed.
	04/05/2021 Consensus Review. No change to policy statement. Coding and
	references reviewed.
	03/30/2022 Consensus Review. No change to policy statement. Policy
	guidelines and references updated. Coding reviewed.
	03/16/2023 Consensus Review. No change to policy statement. Updated
	policy guidelines, and references.
	03/04/2024 Consensus Review. No change to policy statement. Policy
	Guidelines and Background updated. References added.
	02/13/2025 Consensus Review. No change to policy statement. Policy
	Guidelines updated.

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BlueShield Association. Communications issued by Capital Blue Cross in its capacity as administrator of programs and provider relations for all companies.