Anthem

Clinical UM Guideline

Subject:	Genetic Testing for CHARGE Syndrome		
Guideline #:	CG-GENE-09	**Publish Date:**	04/07/2021~~04/15/2020~~
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Description

This document addresses genetic testing for CHARGE syndrome, a rare genetic condition associated with multiple congenital anomalies. The diagnosis is typically made based on clinical findings. The only gene currently known to be associated with the syndrome, chromodomain helicase DNA binding protein (CDH7), is present in most individuals with the condition. Clinical findings may be variable; however, the phenotype cannot be predicted from the genotype.

Note: For additional information regarding related genetic topics, please see the following:

- CG-GENE-13 Genetic Testing for Inherited Diseases
- CG-MED-88 Preimplantation Genetic Diagnosis Testing

Clinical Indications

Medically Necessary:

A. Preimplantation, preconception or in-utero genetic testing for CHARGE syndrome is considered **medically necessary** to rule out a disease-causing mutation when **all** of the following criteria have been met:
   1. The individual being tested has a family history of a first-degree relative with CHARGE syndrome; **and**
   2. Genetic counseling, which encompasses **all** of the following components, has been performed:
      a. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
      b. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
      c. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
      d. Counseling for the psychological aspects of genetic testing.

B. Genetic testing for CHARGE syndrome is considered **medically necessary** to confirm a suspected diagnosis of CHARGE syndrome when **all** of the following criteria have been met:
   1. The individual is an infant or child suspected of having CHARGE syndrome; **and**
   2. Some, but not all, clinical features of CHARGE syndrome are present; **and**

3. Genetic counseling, which encompasses **all** of the following components, has been performed:
   a. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
   b. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
   c. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
   d. Counseling for the psychological aspects of genetic testing.

Not Medically Necessary:

Genetic testing for CHARGE syndrome is considered **not medically necessary** in all other situations.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT

81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) [when specified as the following to detect a specific CHD7 gene variant]: • Known familial variant not otherwise specified, for gene listed in Tier 1 or Tier 2, or identified during a genomic sequencing procedure, DNA sequence analysis, each variant exon
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) [when specified as the following]: • *CHD7 (chromodomain helicase DNA binding protein 7)* (eg, CHARGE syndrome), full gene sequence

ICD-10 Diagnosis

All diagnoses, including but not limited to the following:

Q89.8	Other specified congenital malformations [when specified as CHARGE syndrome]

When services are Not Medically Necessary:

For the procedure codes listed above when criteria are not met or for situations designated in the Clinical Indications section as not medically necessary.

Discussion/General Information

CHARGE syndrome is a rare and complex genetic condition due to the wide range of tissues/systems affected by mutations in the CHD7 gene (Hsu, 2014). It occurs in about one in every 15-17,000 births (van Ravenswaaij-Arts 2015). CHD7 is the only gene currently known to be associated with CHARGE syndrome. In rare cases, an affected person inherits the mutation from an affected parent.

The term CHARGE comes from the first letter of some of the more common features seen in these children:

(C) = coloboma (usually retinochoroidal) and cranial nerve defects (80-90%)
(H) = heart defects in 75-85%, especially tetralogy of Fallot
(A) = atresia of the choanae (blocked nasal breathing passages) (50-60%)
(R) = retardation of growth (70-80%) and development
(G) = genital underdevelopment due to hypogonadotropic hypogonadism
(E) = ear abnormalities and sensorineural hearing loss (>90%)

Four features are almost always present in those with the CHD7 mutation found in CHARGE syndrome: external ear anomalies, cranial nerve dysfunction, semicircular canal hypoplasia, and delayed attainment of motor milestones (Bergman, 2011). The established clinical criteria can provide a diagnosis of definite CHARGE syndrome in many cases, but due to associated variable phenotypes, some individuals may not have all clinical features present and be categorized as having possible or probable CHARGE syndrome.

Genetics

The typical combinations of clinical features seen in CHARGE syndrome are caused by autosomal dominant mutations in the CHD7 gene, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Sequence analysis of the CHD7 coding region detects mutations in many individuals with CHARGE syndrome. Penetrance in those with CHD7 mutations is 100%, meaning that all persons who are heterozygous for a CHD7 mutation have some features of CHARGE syndrome. More than 500 specific CHD7 mutations associated with CHARGE syndrome have been identified (Kim, 2014).

Risk to Family Members

CHARGE syndrome is most often related to a new mutation in the CHD7 gene and occurs in persons with no family history of the disorder. In rare cases, an affected individual inherits the mutation from an affected parent. Some investigators (Hughes, 2014) have proposed that family history (any first-degree relative with at least one major feature of CHARGE) be incorporated into the clinical diagnosis of CHARGE syndrome as a major diagnostic criterion.

Parents of a proband

Most individuals diagnosed with CHARGE syndrome do not have an affected parent. In rare instances, one parent may have mild features, including more than one major characteristic, in addition to minor criteria, such as a cardiovascular malformation (Bergman, 2011). In some cases, a family history may appear negative for the syndrome because of failure to recognize mild features in family members.

Siblings of a proband

The risk to the siblings of the proband depends on the genetic status of the proband's parents. If a parent of the proband is affected or has a CHD7 mutation, the risk to the siblings of inheriting the mutation is 50%. If neither parent is affected, the risk to siblings of a proband is approximately 1%-2%, due to germline mosaicism. Because CHD7 mutation typically occurs as the result of a new mutation, the risk to the siblings of a proband is slight. However, several sibling pairs born to unaffected parents have been reported (Jongmans, 2006; Lalani, 2006) with likely germline mosaicism, confirmed in 2009 by Pauli and colleagues.

Offspring of a proband

Severely affected individuals with CHARGE syndrome do not reproduce. Each child of a mildly affected individual with CHARGE syndrome has a 50% chance of inheriting the mutation. The severity of CHARGE syndrome in a parent does not predict the severity of CHARGE syndrome in the offspring. Variable expression has been observed in familial cases.

Other family members of a proband

The risk to other family members depends on the genetics of the proband's parents. If a parent has the disease-causing mutation in CHD7, then his or her family members may be at risk.

Analytic and Clinical Validity

Blake and colleagues (2011) report that the analytic sensitivity and specificity for detecting mutations in the CHD7 gene are high. In addition, the clinical sensitivity and specificity are also high. Among individuals with a clinical diagnosis of definite CHARGE syndrome, 90-95% have a mutation of CHD7. For those with possible or probable CHARGE syndrome, CHD7 analysis is positive for a mutation in 65-70% of cases. However, laboratories subject to referral bias may lead to lower rates of positive findings. One group reported a 32% detection rate in commercially obtained samples (Bartels, 2010). Another group reported a detection rate of 40.5% (Vuorela, 2007).

Clinical Utility

Many cases of CHARGE syndrome can be diagnosed clinically using established criteria. However, mildly affected persons may only have one or a few of the features of CHARGE syndrome present making diagnosis uncertain. The clinical diagnosis may also be difficult to determine if clinical features are overlapping with other syndromes.

Confirming the diagnosis of CHARGE syndrome with genetic testing may lead to changes in clinical management for those with uncertain clinical features. Additionally, preimplantation, preconception or in-utero genetic testing may be helpful to assist reproductive decision making if there is a family history of a first-degree relative with the disease.

Summary

Established clinical criteria can provide a definite diagnosis of CHARGE syndrome in some cases; however, due to variable phenotypes this may not be possible in others. CHD7 is the only gene currently known to be associated with this syndrome. The clinical utility of making a definite diagnosis of CHARGE syndrome through genetic testing is high, in that confirming a diagnosis with genetic testing may lead to changes in clinical assessment, treatment recommendations and reproductive decisions. The criteria within this document for genetic testing for CHARGE syndrome are consistent with generally accepted standards of medical practice and are clinically appropriate for the indications described in the Clinical Indications section of this document.

Genetic testing for CHARGE syndrome is a laboratory-developed test and does not require United States Food and Drug Administration (FDA) approval. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

Genetic Counseling

According to the National Society of Genetic Counselors (NSGC), genetic counseling is the process of assisting individuals to understand and adapt to the medical, psychological and familial ramifications of a genetic disease. This process typically includes the guidance of a specially trained professional who:

1. Integrates the interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
2. Provides education about inheritance, genetic testing, disease management, prevention and resources; **and**
3. Provides counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
4. Provides counseling for the psychological aspects of genetic testing (NSGC, 2006).

Definitions

First-degree relative: Any relative who is a parent, sibling, or offspring of another.

Genotype: The genetic composition of a cell or organism. May also refer to the specific set of alleles inherited at a locus.

Mutation: A permanent, transmissible change in genetic material.

Penetrance: The proportion of persons with a mutation causing a particular disorder who display clinical symptoms of that disorder. This most often refers to autosomal dominant conditions.

Phenotype: The observable physical and/or biochemical characteristics of the expression of a gene; the clinical presentation of an individual with a particular genotype.

Proband: A term used in medical genetics to refer to the first affected family member with a known pathogenic genetic mutation.

References

Peer Reviewed Publications:

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15. Zentner GE, Layman WS, Martin DM, Scacheri PC. Molecular and phenotypic aspects of CHD7 mutation in CHARGE syndrome. Am J Med Genet A. 2010; 152A:674–686.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Board of Genetic Counselors. Practice-Based Competencies for Genetic Counselors. Available at: http://www.gceducation.org/wp-content/uploads/2019/06/ACGC-Core-Competencies-Brochure_15_Web_REV-6-2019.pdf. ~~http://gceducation.org/Documents/ACGC%20Core%20Competencies%20Brochure_15_Web.pdf.~~ Accessed on ~~January 12~~December 08, 2020.
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3. National Society of Genetic Counselors' Definition Task Force, Resta R, Biesecker BB, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. J Genet Couns. 2006; 5(2):77-83.

Websites for Additional Information

1. CHARGE Syndrome Foundation. About CHARGE. Available at: https://www.chargesyndrome.org/about-charge/overview/. Accessed on ~~January 12~~December 08, 2020.

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Charge Syndrome Genetic Testing
CHD7 Exon Sequencing
CHD7 Full Gene Sequencing
CHD7 Gene Deletion/Duplication
CHD7 Mutation Analysis

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action

Reviewed	02/11/2021	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Description, References and Websites sections. Reformatted Coding section.
Revised	02/20/2020	~~Medical Policy & Technology Assessment Committee (~~MPTAC~~)~~ review. Clarified Clinical Indications section. Updated Description, References and Websites sections.
New	03/21/2019	MPTAC review. Moved content of GENE.00040 Genetic Testing for CHARGE syndrome to a new clinical utilization management guideline document with the same title. References section was updated.