BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.106 Genetic Testing for CHARGE Syndrome

Annual Effective Policy Date: July 1, 2024

Original Policy Date: December 2013

Related Policies:

None

Genetic Testing for CHARGE Syndrome

Description

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 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.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing improves the net health outcome for individuals with suspected CHARGE syndrome.

POLICY STATEMENT

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 section).

Genetic testing for CHARGE syndrome is considered **investigational** in all other situations.

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, and 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.

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 Organisation, and the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the 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.

Table PG1. Nomenclature to Report on Variants Found in DNA

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

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 significance	Change in DNA sequence with uncertain effects on disease
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 for Molecular Pathology.

Genetic Counseling

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

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient"s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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 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.

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 an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Bergman et al (2011) proposed guidelines for *CHD7* analysis and stated that, while the diagnosis of CHARGE syndrome remains primarily a clinical diagnosis (Table 1), molecular testing can confirm the diagnosis in mildly affected patients.[6,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2013	New Policy	Genetic testing for CHARGE syndrome may be considered medically necessary to confirm a diagnosis in a patient with signs/symptoms of CHARGE syndrome, but when a definitive diagnosis cannot be made with clinical criteria. Investigational in all other situations.
December 2014	Replace Policy	Policy updated with literature review. References 7-8, 10-11 added. Policy statement unchanged.
June 2018	Replace Policy	Policy updated with literature review through December 11, 2017;reference 6 added. Policy statements unchanged.
June 2019	Replace Policy	Policy updated with literature review through December 14, 2018; no reference added. This policy is revised with updated format. Policy statements unchanged
June 2020	Replace Policy	Policy updated with literature review through December 9, 2019; no references added. Policy statements unchanged.
June 2021	Replace Policy	Policy updated with literature review through November 17, 2020; no references added. Policy statements unchanged.
June 2022	Replace Policy	Policy updated with literature review through December 9, 2021; reference added. Policy statements unchanged.
June 2023	Replace Policy	Policy updated with literature review through December 6, 2022; references added. Minor editorial refinements to policy statements; intent unchanged.
June 2024	Replace Policy	Policy updated with literature review through December 21, 2023;no references added. Policy statements unchanged.