CHARGE Syndrome and CHD7 Disorder Genetic Testing

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CHARGE Syndrome and CHD7 disorder genetic testing are addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
CHD7 deletion/duplication analysis	81479
CHD7 known familial mutation analysis	81403
CHD7 sequencing	81407

Criteria

Requests for CHD7 genetic testing are reviewed using the following criteria.

CHD7 Known Familial Mutation Analysis

- Genetic Counseling
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing
  - No previous genetic testing of CHD7 that would detect the familial mutation, AND
- Diagnostic Testing for Symptomatic Individuals
  - Known family mutation in CHD7 in 1st degree biological relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CHD7 Sequencing

- Genetic Counseling

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  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing
  - No previous CHD7 sequencing, and
  - No known CHD7 mutation in the family, and
  - Chromosomal microarray, if performed, was negative, AND
- Diagnostic Testing for Symptomatic Individuals
  - The member is suspected to have CHARGE syndrome, but the diagnosis is in question because member meets ONLY ONE of the following using the Blake or Verloes criteria (see Table: *Clinical Diagnostic Criteria for Typical CHARGE Syndrome*, below)
    - 2 major criteria and 1 minor criterion, or
    - 2 major criteria and 0 minor criteria, or
    - 1 major criterion and 3 minor criteria, AND
- Molecular test results will impact medical management, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CHD7 Deletion/Duplication Analysis

- Genetic Counseling
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing
  - No previous CHD7 deletion/duplication testing, and
  - Previous CHD7 sequencing was performed and was negative, and
  - No known CHD7 mutation in the family, and
- Diagnostic Testing for Symptomatic Individuals
  - The member meets the above criteria for CHD7 sequencing, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

What is CHARGE Syndrome/CHD7 disorder?

CHARGE syndrome is a clinically variable syndrome involving multiple congenital anomalies of diverse organ systems.[1] The phenotype has been expanded to CHD7 disorder, which encompasses the full spectrum of clinical findings in individuals with pathogenic CHD7 mutations. This guideline focuses on CHARGE syndrome, as the majority of individuals found to have CHD7 mutations have clinical findings typical of CHARGE syndrome.[2]

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Incidence

CHARGE syndrome occurs in approximately 1/10,000 newborns with an estimated range of 1/8,500 – 1/15,000.[1-3] The disorder is pan-ethnic.[3]

Symptoms

CHARGE was the acronym initially used to describe an association of eye colobomas, heart defects, choanal atresia, growth retardation, genital anomalies, and ear malformations.[1] Following the discovery that heterozygous CHD7 variants cause CHARGE syndrome, molecular genetic testing of family members of probands with CHARGE syndrome expanded the phenotypic spectrum to include phenotypes that do not fulfill the previously proposed CHARGE syndrome clinical diagnostic criteria.[1,2] Additional symptoms associated with CHD7-related disorder phenotype include cleft lip and/or palate, developmental delay, hearing loss, cranial nerve anomalies, vestibular defects, hypothyroidism, hypogonadotropic hypogonadism, tracheoesophageal anomalies, brain anomalies, seizures, renal anomalies, and characteristic dysmorphic facial features.[1,2] Thus, CHD7 disorder exhibits a high degree of clinical variability even among individuals in the same family and among individuals from different families with the same pathogenic variant.[1,2] Given this variability, the presence of a CHD7 mutation is "not equivalent to a diagnosis of CHARGE syndrome."[2]

Cause

CHARGE syndrome and CHD7 disorder are caused by mutations in the CHD7 gene. This gene plays a role in guidance of neural crest cell migration.[4] Sequencing the CHD7 gene will find a causative mutation in 98% of affected individuals.[2] Approximately 2% of mutations identified in CHD7 are whole or partial gene deletions.[2]

Inheritance

CHARGE syndrome and CHD7 disorder are considered autosomal dominant disorders. Although some cases of parent to child transmission of CHARGE syndrome have been reported, most cases are simplex (the only case in the family) and CHD7 mutations, if identified, are typically de novo.[1,2]

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

If neither parent is affected, there is a 1-2% risk of recurrence, most likely due to germline mosaicism.[2]

Diagnosis

Two common sets of clinical diagnostic criteria for CHARGE syndrome have been described.[1] The Blake criteria (first published in 1998 and updated in 2009) set out major and minor diagnostic criteria to be used in diagnosing typical CHARGE syndrome.[5,6] The Verloes criteria provide a means of diagnosing typical CHARGE syndrome (see Table), as well as minor presentations termed partial CHARGE (criteria: 2 major and 1 minor) and atypical CHARGE (criteria: 2 major and 0 minor or 1 major and 3 minor).[7] There are no clinical diagnostic criteria for the phenotypic spectrum associated with CHD7 disorder.

Clinical Diagnostic Criteria for Typical CHARGE Syndrome (Adapted from Bergman et al 2011)[1]

Criteria Set	Major Criteria	Minor Criteria
Blake[5,6] (4 Major or 3 Major and 3 Minor)	Coloboma or microphthalmia Choanal atresia or stenosis External ear anomaly/ middle ear malformation/ mixed sensorineural deafness Cranial nerve dysfunction	Cardiac defect Tracheo-esophageal defects Genital hypoplasia or delayed puberty Cleft lip and/or palate Developmental delay Growth retardation Characteristic facial features
Verloes[7] (3 Major or 2 Major and 2 Minor)	Ocular coloboma Choanal atresia Hypoplastic semicircular canals of the inner ear	Cardiac or esophageal malformation Malformation of the middle or external ear Rhombencephalic dysfunction including sensorineural deafness Hypothalamo-hypophyseal dysfunction (gonadotropin or growth hormone deficiency) Intellectual disability

Management

Management of CHARGE syndrome and CHD7 disorder is based on the variable clinical manifestations. Airway management and cardiac assessment are essential in the newborn period, as is addressing feeding and growth difficulties.[2] Other recommended evaluations and surveillance include the following:[2]

- Ophthalmologic assessment
- Audiologic assessment
- ENT assessment, including imaging to assess middle and inner ear defects
- Genitourinary assessment, including renal ultrasound
- Endocrine evaluation if puberty is delayed or if there is presence of genital anomalies
- Cranial nerve assessment / swallowing studies
- Gastrointestinal assessment for esophageal atresia or trachea-esophageal fistula
- Developmental assessment

Survival

"Life expectancy highly depends on the severity of manifestations; mortality can be high in the first few years when severe birth defects (particularly complex heart defects) are present and often complicated by airway and feeding issues. In childhood, adolescence, and adulthood, decreased life expectancy is likely related to a combination of residual heart defects, infections, aspiration or choking, respiratory issues including obstructive and central apnea, and possibly seizures. Despite these complications, the life expectancy for many individuals can be normal."[2]

Test Information

Testing for CHARGE syndrome and CHD7 disorder may include known familial mutation analysis, next generation sequencing, or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA

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simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and Evidence

Selected Relevant Publications

van Ravenswaaij-Arts et al., 2022

An expert authored review updated in 2022 stated:[2]

- “With the current widespread use of multigene panels and comprehensive genomic testing, it has become apparent that the phenotypic spectrum of heterozygous CHD7 pathogenic variants has broadened to encompass CHARGE syndrome as well as subsets of features that comprise the CHARGE syndrome phenotype ."
- “CHD7 disorder, refers to the entire phenotypic spectrum that can be associated with heterozygous CHD7 pathogenic variants and emphasizes both the need to evaluate an individual found to have a CHD7 pathogenic variant for medically actionable manifestations in the entire phenotypic spectrum (regardless of clinical findings that prompted molecular genetic testing) and the importance of counseling families that the finding of a CHD7 pathogenic variant is not equivalent to a diagnosis of CHARGE syndrome."
- “The diagnosis of CHD7 disorder is established in a proband with suggestive clinical and imaging findings and a heterozygous pathogenic variant in or deletion of CHD7 identified by molecular genetic testing."
- "Sequence analysis of CHD7 is performed to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications and/or chromosomal microarray (CMA) to detect whole-gene deletions."

- “Because CHD7 disorder typically includes multiple congenital anomalies, it is also reasonable to pursue chromosomal microarray testing first, unless classic features of CHD7 disorder (e.g., the CHARGE syndrome phenotype) are apparent."
- “Management of the manifestations of CHD7 disorder can be complex and require a multidisciplinary approach involving clinicians, therapists, and educators."
- “Requires routine follow up of manifestations identified in infancy/childhood, as well as ongoing monitoring of growth, development, educational progress, behavior, and possible endocrine issues."
- “Because of the increased risk of post-anesthesia airway complications, procedures requiring anesthesia should be minimized and combined whenever possible."

van Ravenswaaij-Arts and Martin, 2017

In a review of the etiology and diagnosis, van Ravenswaaij-Arts and Martin stated:[8]

- "In clinically typical individuals with CHARGE syndrome, the tests of first choice are CHD7 Sanger sequencing and chromosomal microarray to screen for deletions and/or MLPA to test for exonic-deletions."
- "CHD7 pathogenic variants have been described in very mildly affected individuals, for example, individuals with isolated hypogonadotropic hypogonadism [HH] due to CHD7 missense variants."
- "It is recommended that individuals with HH and a CHD7 variant be clinically screened for CHARGE syndrome features such as balance problems and deafness, amongst [sic] others."
- "One to two percent of individuals who test positive have an intragenic or whole CHD7 gene deletion that can be detected by microarray analysis, although for small exonic deletions, MLPA is preferred."
- "Most individuals with CHARGE syndrome are sporadic, but recurrence has been documented. ... Parent-child transmission with a recurrence risk of 50% is predominantly seen in milder presentations of the syndrome, although intrafamilial variability is high and a mildly affected parent does not exclude a more severely affected child. If the pathogenic CHD7 variant of a proband cannot be detected in leukocyte DNA of the parents, there remains a 1-2% recurrence risk due to germline mosaicism."

Hefner and Fassi, 2017

In a review of genetic counseling issues in CHARGE syndrome, Hefner and Fassi stated:[9]

- "[Genetic counseling] is particularly important in CS [CHARGE syndrome], as it is extremely complex and variable in its presentation and in its natural history."

- "Despite the identification of pathogenic CHD7 variants in the majority of cases, the diagnosis of CS remains clinical...with genetic testing being particularly helpful in borderline clinical cases."
- "As CS can affect any organ system in the body, the features overlap with countless other syndromes. The top candidates in the differential diagnosis of CS are 22q11.2 deletion syndrome (22q) and Kabuki syndrome (KS). VACTERL association also has a good deal of overlap, but typically does not have significant dysmorphic features."
- "CMA is often performed initially for fetuses or infants with multiple anomalies. This is reasonable as 22q is far more common than CS and CMA can identify other rare microdeletions or microduplications with overlapping features."
- "If CMA is nondiagnostic, CHD7 genetic testing (sequencing and deletion/duplication analysis) is recommended in the presence of any major feature of CS with multiple anomalies. If CHD7 analysis is nondiagnostic, whole exome sequencing (WES) may be considered."
- "Every individual with CS has his or her own unique set of medical and developmental issues. Medical management of CS involves comprehensive monitoring of multiple organ systems by a multitude of specialists."
- "Appropriate therapies will involve not only traditional therapies (occupational, physical, speech, and language therapies, etc.) but require the expertise of DB [deafblind] specialists. DB specialists are professionals expert in the unique needs of children with multiple sensory impairments."
- Genetic counseling should include information on prognosis including mortality, morbidity, and sensory, motor and intellectual expectations.

Bergman et al., 2011

In addressing molecular testing for CHARGE syndrome, Bergman and colleagues suggested that CHD7 testing, including sequencing and deletion analysis, should be considered in individuals with:[1]

- 3 cardinal features
- 2 cardinal features and 1 supportive feature
- 2 cardinal features if imaging shows semicircular canal abnormalities
- 1 cardinal feature and 1 supportive feature if imaging shows semicircular canal abnormalities

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for CHARGE syndrome and CHD7 disorder testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the

condition, but have non-standard features, will not receive an immediate approval for testing.

References

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