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Genetic Testing for CHARGE Syndrome

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I. Policy Description

CHARGE (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities) syndrome is a multiple congenital anomaly condition affected by mutations in the *CHD7* gene.[1] The majority of these mutations result in a wide range of congenital anomalies that include colobomas (congenital absence of pieces of tissue in eye structures that may cause defects in the iris, retina, or optic nerve); heart defects; choanal atresia (an obliteration or blockage of the posterior nasal aperture due to a persistent oronasal membrane that prevents joining of the nose and oropharynx); retarded growth and development; genital hypoplasia; ear anomalies; and deafness.[2-4]

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) To confirm a diagnosis in a patient with signs/symptoms of CHARGE (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities) syndrome when a definitive diagnosis cannot be made with clinical criteria, genetic testing for the presence of *CHD7* variants **MEETS COVERAGE CRITERIA**.

2) For asymptomatic individuals who have a first-degree relative (see Note 1) diagnosed with CHARGE syndrome who have a known pathogenic/likely pathogenic (P/LP) variant, genetic testing restricted to the known familial *CHD7* variant **MEETS COVERAGE CRITERIA**.

3) For individuals seeking prenatal or pre-implantation screening, genetic testing for the presence of *CHD7* variants **MEETS COVERAGE CRITERIA**.

4) For individuals with clinical features of CHARGE syndrome who have already tested negative for P/LP variants in *CHD7*, screening for variants in *ZEB2, KMT2D* and *EFTUD2* **MEETS COVERAGE CRITERIA.**

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

5) For all other situations not discussed above, genetic testing for CHARGE syndrome **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note 1: First-degree relatives include parents, full siblings, and children of the individual.

III. Table of Terminology

Term	Definition
ATP	Adenosine triphosphate
CHARGE	Coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities
CHD7	*Chromodomain helicase deoxyribonucleic acid binding protein 7*
CHH	Congenital hypogonadotropic hypogonadism
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CN	Cranial nerve
CN I	Cranial nerve absent or reduced sense of smell
CN IX, X	Cranial nerve swallowing problem
CN V	Cranial nerve weak chewing/swallowing
CN VII	Cranial nerve facial palsy
CN VIII	Cranial nerve sensorineural hearing loss and balance/ vestibular problems
DNA	Deoxyribonucleic acid
EFTUD2	*Elongation factor Tu GTP binding domain containing 2*
ENT	Ear, nose, and throat
EP300	*E1A binding protein p300*
FDA	Food and Drug Administration
GI	Gastrointestinal
GnRH	*Gonadotropin-releasing hormone*
HH	Hypogonadotropic hypogonadism
KMT2D	*Lysine methyltransferase 2D*
LDTs	Laboratory-developed tests
MLPA	Multiplex ligation-dependent probe amplification
NGS	Next-generation sequencing
NIPT	Non-invasive prenatal test
NORD	National Organization for Rare Disorders
PUF60	*Poly(U) binding splicing factor 60*
RERE	*Arginine-glutamic acid dipeptide repeats*
SNP	Single nucleotide polymorphism
SWI-SNF	Switch/sucrose non-fermentable
TBX1	*T-box transcription factor 1*

ZEB2	*Zinc finger E-box binding homeobox 2*

IV. Scientific Background

CHARGE (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities) syndrome is a relatively common cause of congenital anomalies affecting approximately 1 in 8,500 to 10,000 births.[5] First described by Hall (1979) and Hittner, et al. (1979), CHARGE syndrome was diagnosed clinically[8,9] until causative mutations were identified in the *CHD7* (Chromodomain-helicase-DNA-binding protein 7/ATP-dependent helicase CHD7) gene.[10] Due to the variability associated with *CHD7* mutations, genetic analysis may be helpful for genotypic diagnostics but will not necessarily assist in phenotypic predictions.[11] Most cases of CHARGE syndrome occur through spontaneous mutation of the *CHD7* gene; however, the disorder can also be passed from parent to offspring in an autosomal dominant fashion.[12]

The *CHD7* gene contains 38 exons that encode for the 300-kDa CHD7 chromatin remodeler protein.[13] The CHD7 protein is a member of the SWI-SNF superfamily of ATP-dependent chromatin remodelers that bind to DNA and modulate gene expression.[14,15] CHD7 has an important, dosage-dependent role in the development of several craniofacial tissues[16] and has also been found to assist with orchestrating neural crest and central nervous system development.[17-20] Further, *CHD7* plays a role in additional gene expression programs and cellular interactions during embryogenesis; this likely occurs through the dysregulation of co-transcriptional alternative splicing.[21-23]

It is worth noting that the CHARGE syndrome acronym does not cover all disorders that may result from this disease; a diagnosis may include additional sensory deficits and birth defects, including cranial nerve dysfunction and feeding and gastrointestinal (GI) dysfunction.[24] It is notable that more than 90% of patients experience feeding and GI dysfunction; this is known to cause significant morbidity and mortality in the CHARGE syndrome patient population.[24,25] Further, many CHARGE syndrome patients exhibit clival pathology, such as coronal clefts; this is now considered a useful diagnostic criteria for patients.[26] Nonetheless, the range of mutations in the *CHD7* gene results in a broad phenotype that may involve almost all organ and sensory systems in the body, therefore causing significant variabilities in severity and comorbidity.[27] Hence, no single feature is universally present or sufficient for the clinical diagnosis of CHARGE syndrome.

Clinical Validity

The initial clinical CHARGE syndrome diagnostic criteria[8] was first adapted to include supplemental clinical abnormalities.[28] More recently, the diagnostic criteria were updated to incorporate results of molecular testing.[29] Most individuals (90-95%) fulfilling the clinical criteria for a CHARGE syndrome diagnosis have a *CHD7* variant that is detectable by Sanger sequencing or next-generation sequencing (NGS).[11,30] However, since the inclusion of *CHD7*, variants have been described in 14-17% of mildly affected individuals who would not meet the clinical criteria for a CHARGE syndrome diagnosis.[11] This has resulted in the addition of *CHD7* to NGS gene panels for developmental delay, colobomata, heart defects,[31] and other congenital malformations.[32] The clinical validity of genetic testing that relies on identifying *CHD7* gene mutations may create issues in the future; van Ravenswaaij-Arts and Martin (2017) stated that individuals with a missense variant of the *CHD7* gene will less often fulfill clinical

criteria for a CHARGE syndrome diagnosis, since there may be a decreased prevalence of congenital heart defects and choanal atresia with a missense variant. However, this type of variant is overrepresented in families with parent to child transmission of CHARGE syndrome.[32]

Despite the availability of molecular diagnostic tools, "the cause of CHARGE syndrome remains unclear in approximately 5-10% of typical CHARGE patients and in 40-60% of suspected cases."[30] Other genetic conditions such as 22q11.2 deletion (DiGeorge) syndrome, Kallmann syndrome, and Kabuki syndrome are known to have an overlapping phenotypic spectrum with CHARGE syndrome,[30] which may complicate diagnosis based strictly on clinical criteria. Additionally, it is challenging to distinguish younger patients with Kabuki syndrome from those with CHARGE syndrome since they lack the facial gestalt of Kabuki syndrome but show similar organ malformations to those of CHARGE syndrome patients.[33]

A more recent study utilized whole exome sequencing to genetically analyze 28 individuals exhibiting CHARGE syndrome features. Pathogenic variants in *CHD7*, other genes (*RERE, KMT2D, EP300, PUF60)*, and no pathogenic variants were found in 53.6%, 14.3%, and 28.6% of participants, respectively.[34] Based on these results, it was suggested that "the phenotypic features of CHARGE syndrome overlap with multiple other rare single-gene syndromes."[34]

In a study by Gonçalves, et al. (2019), mutations in the *CHD7* gene were observed in patients with isolated congenital hypogonadotropic hypogonadism (CHH), a condition that is characterized by the lack of normal pubertal development resulting from deficient gonadotropin-releasing hormone (GnRH). This demonstrates a limitation to clinical validity in *CHD7* genetic testing for CHARGE syndrome. The variable phenotypic expression is related to the type of mutation, as CHARGE syndrome patients seem to have "typically highly deleterious protein-truncating mutations, whereas *CHD7* mutations in isolated CHH are typically missense."[35]

A study conducted by Qin, et al. (2020) also found five neonatal patients to have drastically different clinical CHARGE syndrome phenotypes, with postnatal dyspnea as the most prominent symptom in the study cohort. The study found three novel genetic variants (c.2828_2829delAG, c.4667dupC, and c.7873C > T) and two reported variants (c.4667dupC and c.1480C > T) using whole exome sequencing that contributed to CHARGE syndrome clinical presentations. In accordance with this data, researchers concluded that though prenatal diagnosis of CHARGE syndrome may continue to be a challenge, "fetal *de novo* mutations screening by non-invasive prenatal test (NIPT) with maternal plasma is highly efficient for diagnosis. Detection of mutations in E1 and E38 may also provide clues for predicting severity of CHARGE syndrome by NIPT with maternal plasma."[36]

Another study was completed with data from 145 participants, all of whom were previously clinically diagnosed with CHARGE syndrome. Researchers surveyed these participants to determine if they had completed genetic testing to confirm a CHARGE syndrome diagnosis. Of the total survey participants, 68% had never received genetic testing; of the 46 patients who did complete genetic testing, 74% tested positive for a *CHD7* mutation.[37]

Clinical Utility and Validity

Patients with CHARGE syndrome experience a wide spectrum of comorbidities, some more severe than others, and the complex management of these comorbidities can often lead to more issues. The clinical utility of making a definite diagnosis of CHARGE syndrome is high since a confirmed CHARGE diagnosis will lead to changes in clinical management, including well-defined clinical assessment and treatment recommendations.[27,38] No consensus on the utility of genetic testing in patients who present with a clear clinical diagnosis exists. However, testing may be useful in patients who do not have the classical CHARGE characteristics and may be at risk for the long-term complications of CHARGE syndrome.[39] For instance, many patients with CHARGE syndrome will often have more than one dysfunctional cranial nerve (CN), which can manifest as an absent or reduced sense of smell (CN I), weak chewing/swallowing (CN V), facial palsy (CN VII), sensorineural hearing loss (CN VIII), balance/vestibular problems (CN VIII), and swallowing problems (CN IX, X).[40] Testing is recommended in all suspected cases of CHARGE syndrome, especially in patients who partially meet the clinical criteria.[11,29,38]

Hefner and Fassi (2017) state that a CHARGE syndrome diagnosis "should be considered in patients with any of the major diagnostic features: coloboma, choanal atresia, semicircular canal anomalies, or cranial nerve anomalies." These features are also common in 22q11.2 deletion (DiGeorge) and Kabuki syndromes, and genetic testing may be used to distinguish between these conditions; further, genetic counseling is an important step in a CHARGE syndrome diagnosis.[25] This will prove to be critical in establishing a multidisciplinary care team for potential developmental concerns of a CHARGE syndrome child, such as combined deafness-blindness.[40] As CHARGE patients grow up, they may have feeding difficulties or orofacial anomalies that may need to be attended to by ENT specialists, cardiovascular malformations that may involve pediatric cardiologists, or concomitant hypogonadotropic hypogonadism (HH) that may require the help of pediatric endocrinologists, supporting the high clinical utility of *CHD7* testing of CHARGE syndrome.[41]

V. Guidelines and Recommendations

The CHARGE Syndrome Foundation

The CHARGE Syndrome Foundation states that CHARGE syndrome is marked by key features such as coloboma, cranial nerve abnormalities, choanal atresia, heart defects, characteristic external ears, esophageal defects, small/absent semicircular canals, genitourinary abnormalities, and *CHD7* gene mutations, and that its "diagnosis should be made by a Medical Geneticist. Diagnosis is based on key features, ideally with DNA testing for *CHD7* mutations." Though "it does not usually run in families," the "recurrence risk to unaffected parents is 1-2%" and "if a parent has CHARGE Syndrome, the risk to a baby is 50/50."[42]

The National Organization for Rare Disorders (NORD)

The NORD states that "diagnosis can be confirmed by molecular genetic testing identifying the variants in the *CHD7* gene associated with the condition. If no disease-causing variants are found, a SNP chromosomal microarray should be done, because in a few patients, there has been a submicroscopic change in the chromosome 8q12.2 region. If both these tests are negative, whole genome exome sequencing should be done, since other genetic disorders share some clinical features with CHARGE

syndrome, and new variants in the *ZEB2, KMT2D* and *EFTUD2* genes have been found in children previously diagnosed as having CHARGE syndrome."[43]

Other Recommendations

Guidelines by professional societies and organizations about genetic testing for CHARGE syndrome are limited; however, recommendations by subject matter experts in the field are included below.

A comprehensive guideline and clinical checklist were developed by the Atlantic Canadian CHARGE syndrome team. This checklist includes diagnostic criteria such as clinical diagnoses and genetic testing; genetic consultation for *CHD7* analysis and array comparative genomic hybridization is also recommended. Further, the guideline notes that although "there is no consensus on genetic testing in the presence of a clear clinical diagnosis," multiple guidelines recommend genetic testing in "all suspected cases of CHARGE syndrome and especially for patients who partially meet the clinical criteria."[38]

According to guidelines published by researchers at The Children's Mercy Hospitals and Clinics in Kansas City, Missouri, a previously unknown missense mutation in exon 31 of *CHD7* can cause a diagnosis of CHARGE syndrome. This mutation can be inherited, showing that family history should be considered as a major diagnostic criterion for CHARGE syndrome.[44] Moreover, because orofacial clefting is often observed with a diagnosis of CHARGE syndrome, it is also suggested that patients with this anomaly be tested for CHARGE syndrome.[44]

Guidelines published by de Geus, et al. (2017) provide a comprehensive overview of all other published recommendations for CHARGE syndrome and introduce guidelines for cranial imaging. A summary of their recommendations is included in the table below.[27]

Recommendation	References
CHARGE is a clinical diagnosis	8,11,28,45,46
***CHD7* testing can confirm uncertain diagnosis in mildly affected patients**	11
***CHD7* testing may be performed according to a flow diagram**	11
A genome-wide array should be performed in patients with CHARGE syndrome but without a *CHD7* mutation	47
Clinical genetics consultation is indicated, including options for prenatal diagnosis	11
Patients diagnosed with hypogonadotropic hypogonadism and anosmia should be screened for clinical features consistent with CHARGE syndrome	48
Olfactory bulb hypoplasia and semicircular canal aplasia should be considered major signs for CHARGE syndrome	49,50
If a parent has any features of CHARGE syndrome, molecular genetic testing is appropriate if a *CHD7* pathogenic variant has been identified in the proband	51
***CHD7* analysis should be performed in patients with a 22q11.2 deletion phenotype without *TBX1* haploinsufficiency**	47
***CHD7* analysis should be performed in patients with Kallmann syndrome who have at least two additional CHARGE features or semicircular canal anomalies**	48,52,53

CHD7 should be included in massive parallel sequencing gene panels for diagnostics in syndromic heart defects	31
CHD7 analysis should not be performed routinely in patients with only atrial septal defect or conotruncal heart defects	31
CHD7 analysis should not be performed in septo-optic dysplasia patients without features of CHARGE	54
MLPA analysis is indicated if no causal _CHD7_ is mutation is found	55,56
MLPA analysis is not indicated if no _CHD7_ mutation is found	57

Guidelines for clinical diagnosis have also been published by Hale, et al. (2016), which include the identification of a pathogenic *CHD7* variant as major criteria for a CHARGE syndrome diagnosis. In a response to comments received on their publication by,[39] Hale and colleagues reaffirmed the appropriateness of *CHD7* testing under the right circumstances. They state "there are specific (and extremely useful) guidelines for when to test for *CHD7* sequence variants in individuals with CHARGE features.[11] Accurate and meaningful genetic information can lead to improved understanding of etiology, provide accurate recurrence risks, and help pave the way toward better clinical care. We advocate incorporating *CHD7* sequence variant information into the diagnostic algorithm, when it is available, since this information can improve understanding of disease causation, pathogenesis, and treatment options. In cases when *CHD7* variant testing is not available, the diagnosis can still be made based on appropriate clinical assessments."[58]

Bergman, et al. (2011) asserted that *CHD7* testing can confirm uncertain diagnoses in mildly affected patients. Moreover, clinical genetics consultation is also indicated, including options for prenatal diagnosis.

Corsten-Janssen, et al. (2014) published recommendations which state that:

- *CHD7* should be included in massive parallel sequencing gene panels for diagnostics in syndromic heart defects
- *CHD7* analysis should be performed in patients with a 22q11.2 deletion phenotype without *TBX1* haploinsufficiency
- Genome-wide array should be performed in patients with CHARGE syndrome but without a *CHD7* mutation

Jongmans, et al. (2008) and Jongmans, et al. (2009) recommended that:

- Patients diagnosed with hypogonadotropic hypogonadism and anosmia should be screened for clinical features consistent with CHARGE syndrome
- If a parent has any features of CHARGE syndrome, molecular genetic testing is appropriate if a *CHD7* pathogenic variant has been identified in the proband
- *CHD7* analysis should be performed in patients with Kallmann syndrome who have at least two additional CHARGE features or semicircular canal anomalies

Usman and Sur (2025) compiled guidelines for the diagnosis of CHARGE syndrome that state that the "only gene associated with CHARGE syndrome is *CHD7*, encrypting the chromodomain helicase DNA

binding protein. This sequencing detects pathogenic variants in maximum individuals with typical CHARGE syndrome with the following criteria of having the three primary characteristics or four major and three minor characteristics." The major criteria are the 4C's: coloboma, cranial nerve abnormalities, choanal atresia, and typical CHARGE ear. The minor criteria are heart defects, cleft lip or palate, genital abnormalities, hypotonia, kidney abnormalities, esophageal atresia, poor growth, typical CHARGE face, and typical CHARGE hand. The authors summarize the outline of diagnosis as:

- "Clinical diagnosis: It is a combination of major and minor diagnostic characteristics, having the three primary features or four major and three minor characteristics."
- "Laboratory analysis: It includes having the blood workup done, such as complete blood count (CBC), serum electrolytes, renal function test, luteinizing hormone-releasing hormone, Human chorionic gonadotropin (hCG), blood urea nitrogen (BUN), creatinine, growth hormone levels, and immunologic studies."
- "Genetic analysis: Prenatal screening for *CHD7* variants is restricted to familial cases, via amniocentesis chorionic or villus sampling at 10–12 and 18–20 weeks' gestation."
- "Imaging studies: Involves a skeletal survey, abdominal ultrasound, barium swallow, echocardiography, chest x-ray, cranial ultrasound in neonates, and head computed tomography (CT) scan and magnetic resonance imaging (MRI)."[12]

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VIII. Evidence-based Scientific References

1. GARD. Charge syndrome. Updated August 2025. https://rarediseases.info.nih.gov/diseases/29/charge-syndrome
2. Jongmans MC, Admiraal RJ, van der Donk KP, et al. CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene. *J Med Genet*. Apr 2006;43(4):306-14. doi:10.1136/jmg.2005.036061
3. Guercio JR, Martyn LJ. Congenital malformations of the eye and orbit. *Otolaryngol Clin North Am*. Feb 2007;40(1):113-40, vii. doi:10.1016/j.otc.2006.11.013
4. Isaacson GC. Congenital anomalies of the nose. UpToDate, Inc. Updated Oct 02, 2024. https://www.uptodate.com/contents/congenital-anomalies-of-the-nose
5. Longman. *Obstetric Imaging: Fetal Diagnosis and Care*. 2018.
6. Hall BD. Choanal atresia and associated multiple anomalies. *J Pediatr*. Sep 1979;95(3):395-8. doi:10.1016/s0022-3476(79)80513-2
7. Hittner HM, Hirsch NJ, Kreh GM, Rudolph AJ. Colobomatous microphthalmia, heart disease, hearing loss, and mental retardation--a syndrome. *J Pediatr Ophthalmol Strabismus*. Mar-Apr 1979;16(2):122-8. doi:10.3928/0191-3913-19790301-10
8. Blake KD, Davenport SL, Hall BD, et al. CHARGE association: an update and review for the primary pediatrician. *Clin Pediatr (Phila)*. Mar 1998;37(3):159-73. doi:10.1177/000992289803700302
9. Pagon RA, Graham JM, Jr., Zonana J, Yong SL. Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr*. Aug 1981;99(2):223-7. doi:10.1016/s0022-3476(81)80454-4
10. Vissers LE, van Ravenswaaij CM, Admiraal R, et al. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nat Genet*. Sep 2004;36(9):955-7. doi:10.1038/ng1407
11. Bergman JE, Janssen N, Hoefsloot LH, Jongmans MC, Hofstra RM, van Ravenswaaij-Arts CM. CHD7 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype. *J Med Genet*. May 2011;48(5):334-42. doi:10.1136/jmg.2010.087106
12. Usman N, Sur M. CHARGE Syndrome. *StatPearls*. 2025.

13. Bilan F, Legendre M, Charraud V, et al. Complete screening of 50 patients with CHARGE syndrome for anomalies in the CHD7 gene using a denaturing high-performance liquid chromatography-based protocol: new guidelines and a proposal for routine diagnosis. *J Mol Diagn*. Jan 2012;14(1):46-55. doi:10.1016/j.jmoldx.2011.08.003
14. Marfella CG, Imbalzano AN. The Chd family of chromatin remodelers. *Mutat Res*. May 1 2007;618(1-2):30-40. doi:10.1016/j.mrfmmm.2006.07.012
15. Asad Z, Pandey A, Babu A, et al. Rescue of neural crest-derived phenotypes in a zebrafish CHARGE model by Sox10 downregulation. *Hum Mol Genet*. Aug 15 2016;25(16):3539-3554. doi:10.1093/hmg/ddw198
16. Sperry ED, Hurd EA, Durham MA, Reamer EN, Stein AB, Martin DM. The chromatin remodeling protein CHD7, mutated in CHARGE syndrome, is necessary for proper craniofacial and tracheal development. *Dev Dyn*. Sep 2014;243(9):1055-66. doi:10.1002/dvdy.24156
17. He D, Marie C, Zhao C, et al. Chd7 cooperates with Sox10 and regulates the onset of CNS myelination and remyelination. *Nat Neurosci*. May 2016;19(5):678-689. doi:10.1038/nn.4258
18. Whittaker DE, Riegman KL, Kasah S, et al. The chromatin remodeling factor CHD7 controls cerebellar development by regulating reelin expression. *J Clin Invest*. Mar 1 2017;127(3):874-887. doi:10.1172/JCI83408
19. Bajpai R, Chen DA, Rada-Iglesias A, et al. CHD7 cooperates with PBAF to control multipotent neural crest formation. *Nature*. Feb 18 2010;463(7283):958-62. doi:10.1038/nature08733
20. Van Nostrand JL, Brady CA, Jung H, et al. Inappropriate p53 activation during development induces features of CHARGE syndrome. *Nature*. Oct 9 2014;514(7521):228-32. doi:10.1038/nature13585
21. Belanger C, Berube-Simard FA, Leduc E, et al. Dysregulation of cotranscriptional alternative splicing underlies CHARGE syndrome. *Proc Natl Acad Sci U S A*. Jan 23 2018;115(4):E620-E629. doi:10.1073/pnas.1715378115
22. Berube-Simard FA, Pilon N. Molecular dissection of CHARGE syndrome highlights the vulnerability of neural crest cells to problems with alternative splicing and other transcription-related processes. *Transcription*. Sep 11 2018:1-8. doi:10.1080/21541264.2018.1521213
23. Schulz Y, Wehner P, Opitz L, et al. CHD7, the gene mutated in CHARGE syndrome, regulates genes involved in neural crest cell guidance. *Hum Genet*. Aug 2014;133(8):997-1009. doi:10.1007/s00439-014-1444-2
24. Blake KD, Hudson AS. Gastrointestinal and feeding difficulties in CHARGE syndrome: A review from head-to-toe. *Am J Med Genet C Semin Med Genet*. Dec 2017;175(4):496-506. doi:10.1002/ajmg.c.31586
25. Hefner MA, Fassi E. Genetic counseling in CHARGE syndrome: Diagnostic evaluation through follow up. *Am J Med Genet C Semin Med Genet*. Dec 2017;175(4):407-416. doi:10.1002/ajmg.c.31589
26. Mahdi ES, Whitehead MT. Clival Malformations in CHARGE Syndrome. *AJNR Am J Neuroradiol*. Jun 2018;39(6):1153-1156. doi:10.3174/ajnr.A5612
27. de Geus CM, Free RH, Verbist BM, et al. Guidelines in CHARGE syndrome and the missing link: Cranial imaging. *Am J Med Genet C Semin Med Genet*. Dec 2017;175(4):450-464. doi:10.1002/ajmg.c.31593
28. Verloes A. Updated diagnostic criteria for CHARGE syndrome: a proposal. *Am J Med Genet A*. Mar 15 2005;133A(3):306-8. doi:10.1002/ajmg.a.30559

29. Hale CL, Niederriter AN, Green GE, Martin DM. Atypical phenotypes associated with pathogenic CHD7 variants and a proposal for broadening CHARGE syndrome clinical diagnostic criteria. *Am J Med Genet A*. Feb 2016;170A(2):344-354. doi:10.1002/ajmg.a.37435
30. Janssen N, Bergman JE, Swertz MA, et al. Mutation update on the CHD7 gene involved in CHARGE syndrome. *Hum Mutat*. Aug 2012;33(8):1149-60. doi:10.1002/humu.22086
31. Corsten-Janssen N, du Marchie Sarvaas GJ, Kerstjens-Frederikse WS, et al. CHD7 mutations are not a major cause of atrioventricular septal and conotruncal heart defects. *Am J Med Genet A*. Dec 2014;164A(12):3003-9. doi:10.1002/ajmg.a.36747
32. van Ravenswaaij-Arts C, Martin DM. New insights and advances in CHARGE syndrome: Diagnosis, etiologies, treatments, and research discoveries. *Am J Med Genet C Semin Med Genet*. Dec 2017;175(4):397-406. doi:10.1002/ajmg.c.31592
33. Pauli S, Bajpai R, Borchers A. CHARGEd with neural crest defects. *Am J Med Genet C Semin Med Genet*. Dec 2017;175(4):478-486. doi:10.1002/ajmg.c.31584
34. Moccia A, Srivastava A, Skidmore JM, et al. Genetic analysis of CHARGE syndrome identifies overlapping molecular biology. *Genet Med*. Sep 2018;20(9):1022-1029. doi:10.1038/gim.2017.233
35. Gonçalves CI, Patriarca FM, Aragüés JM, et al. High frequency of CHD7 mutations in congenital hypogonadotropic hypogonadism. *Scientific Reports*. 2019/02/07 2019;9(1):1597. doi:10.1038/s41598-018-38178-y
36. Qin Z, Su J, Li M, et al. Clinical and Genetic Analysis of CHD7 Expands the Genotype and Phenotype of CHARGE Syndrome. *Front Genet*. 2020;11:592. doi:10.3389/fgene.2020.00592
37. Hartshorne TS, Stratton KK, van Ravenswaaij-Arts CM. Prevalence of genetic testing in CHARGE syndrome. *J Genet Couns*. Feb 2011;20(1):49-57. doi:10.1007/s10897-010-9328-7
38. Trider CL, Arra-Robar A, van Ravenswaaij-Arts C, Blake K. Developing a CHARGE syndrome checklist: Health supervision across the lifespan (from head to toe). *Am J Med Genet A*. Mar 2017;173(3):684-691. doi:10.1002/ajmg.a.38085
39. Blake K, van Ravenswaaij-Arts CM, Hoefsloot L, Verloes A. Clinical utility gene card for: CHARGE syndrome. *Eur J Hum Genet*. Sep 2011;19(9)doi:10.1038/ejhg.2011.45
40. Hudson A, Trider C-L, Blake K. CHARGE Syndrome. *Pediatrics in Review*. 2017;38(1):56-59. doi:10.1542/pir.2016-0050
41. Dijk DR, Bocca G, van Ravenswaaij-Arts CM. Growth in CHARGE syndrome: optimizing care with a multidisciplinary approach. *J Multidiscip Healthc*. 2019;12:607-620. doi:10.2147/jmdh.S175713
42. CHARGE Syndrome Foundation. CHARGE Syndrome Fact Sheet. https://www.chargesyndrome.org/for-families/new-diagnosis/factsheet/
43. NORD. CHARGE Syndrome. https://rarediseases.org/rare-diseases/charge-syndrome/
44. Hughes SS, Welsh HI, Safina NP, Bejaoui K, Ardinger HH. Family history and clefting as major criteria for CHARGE syndrome. *Am J Med Genet A*. Jan 2014;164a(1):48-53. doi:10.1002/ajmg.a.36192
45. Harris J, Robert E, Kallen B. Epidemiology of choanal atresia with special reference to the CHARGE association. *Pediatrics*. Mar 1997;99(3):363-7. doi:10.1542/peds.99.3.363
46. Issekutz KA, Graham JM, Jr., Prasad C, Smith IM, Blake KD. An epidemiological analysis of CHARGE syndrome: preliminary results from a Canadian study. *Am J Med Genet A*. Mar 15 2005;133a(3):309-17. doi:10.1002/ajmg.a.30560
47. Corsten-Janssen N, Saitta SC, Hoefsloot LH, et al. More Clinical Overlap between 22q11.2 Deletion Syndrome and CHARGE Syndrome than Often Anticipated. *Molecular syndromology*. Jun 2013;4(5):235-45. doi:10.1159/000351127

48. Jongmans MC, van Ravenswaaij-Arts CM, Pitteloud N, et al. CHD7 mutations in patients initially diagnosed with Kallmann syndrome--the clinical overlap with CHARGE syndrome. *Clin Genet*. Jan 2009;75(1):65-71. doi:10.1111/j.1399-0004.2008.01107.x
49. Asakura Y, Toyota Y, Muroya K, et al. Endocrine and radiological studies in patients with molecularly confirmed CHARGE syndrome. *The Journal of clinical endocrinology and metabolism*. Mar 2008;93(3):920-4. doi:10.1210/jc.2007-1419
50. Sanlaville D, Etchevers HC, Gonzales M, et al. Phenotypic spectrum of CHARGE syndrome in fetuses with CHD7 truncating mutations correlates with expression during human development. *J Med Genet*. Mar 2006;43(3):211-217. doi:10.1136/jmg.2005.036160
51. Jongmans MC, Hoefsloot LH, van der Donk KP, et al. Familial CHARGE syndrome and the CHD7 gene: a recurrent missense mutation, intrafamilial recurrence and variability. *Am J Med Genet A*. Jan 1 2008;146A(1):43-50. doi:10.1002/ajmg.a.31921
52. Bergman JE, de Ronde W, Jongmans MC, et al. The results of CHD7 analysis in clinically well-characterized patients with Kallmann syndrome. *The Journal of clinical endocrinology and metabolism*. May 2012;97(5):E858-62. doi:10.1210/jc.2011-2652
53. Costa-Barbosa FA, Balasubramanian R, Keefe KW, et al. Prioritizing genetic testing in patients with Kallmann syndrome using clinical phenotypes. *The Journal of clinical endocrinology and metabolism*. May 2013;98(5):E943-53. doi:10.1210/jc.2012-4116
54. Gregory LC, Gevers EF, Baker J, et al. Structural pituitary abnormalities associated with CHARGE syndrome. *The Journal of clinical endocrinology and metabolism*. Apr 2013;98(4):E737-43. doi:10.1210/jc.2012-3467
55. Wincent J, Holmberg E, Stromland K, et al. CHD7 mutation spectrum in 28 Swedish patients diagnosed with CHARGE syndrome. *Clin Genet*. Jul 2008;74(1):31-8. doi:10.1111/j.1399-0004.2008.01014.x
56. Wincent J, Schulze A, Schoumans J. Detection of CHD7 deletions by MLPA in CHARGE syndrome patients with a less typical phenotype. *European journal of medical genetics*. Jul-Aug 2009;52(4):271-2. doi:10.1016/j.ejmg.2009.02.005
57. Bergman JE, de Wijs I, Jongmans MC, Admiraal RJ, Hoefsloot LH, van Ravenswaaij-Arts CM. Exon copy number alterations of the CHD7 gene are not a major cause of CHARGE and CHARGE-like syndrome. *European journal of medical genetics*. Sep-Oct 2008;51(5):417-25. doi:10.1016/j.ejmg.2008.03.003
58. Hale CL, Niederriter AN, Green GE, Martin DM. Response to correspondence to Hale et al. atypical phenotypes associated with pathogenic CHD7 variants and a proposal for broadening CHARGE syndrome clinical diagnostic criteria. *Am J Med Genet A*. Dec 2016;170(12):3367-3368. doi:10.1002/ajmg.a.37629

IX. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
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)

81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
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)
81479	Unlisted molecular pathology procedure

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

X. Policy History

Action Date	Action
June 01, 2023	Policy created
March 17, 2026	Policy approved by Medical Directors
March 27, 2026	Policy approved at UMC
August 1, 2026	Policy effective date following notification period