Sentara Health Plans

Genetic Testing for CHARGE Syndrome

Policy Number: AHS – M2070 – Genetic Testing for CHARGE Syndrome	Policy Revision Date: 04/01/2025 Initial Policy Effective Date: 12/01/2024

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 (Hsu et al., 2014). 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 (Guercio & Martyn, 2007; Isaacson, 2022; Jongmans et al., 2006).

II. Related Policies

Policy Number	Policy Title
AHS-M2145	General Genetic Testing, Germline Disorders

III. 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 likely pathogenic or pathogenic 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 likely pathogenic or pathogenic 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.

IV. 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*

V. 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 (Longman, 2018). First described by Hall (1979) and Hittner et al. (1979), CHARGE syndrome was diagnosed clinically (Blake et al., 1998; Pagon et al., 1981) until causative mutations were identified in the *CHD7* (Chromodomain-helicase-DNA-binding protein 7/ATP-dependent helicase CHD7) gene (Vissers et al., 2004). Due to the variability associated with *CHD7* mutations, genetic analysis may be helpful for genotypic diagnostics but will not necessarily assist in phenotypic predictions (Bergman et al., 2011). 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 (Usman & Sur, 2024).

The *CHD7* gene contains 38 exons that encode for the 300-kDa CHD7 chromatin remodeler protein (Bilan et al., 2012). The CHD7 protein is a member of the SWI-SNF superfamily of ATP-dependent chromatin remodelers that bind to DNA and modulate gene expression (Asad et al., 2016; Marfella & Imbalzano, 2007). CHD7 has an important, dosage-dependent role in the development of several craniofacial tissues (Sperry et al., 2014) and has also been found to assist with orchestrating neural crest and central nervous system development (Bajpai et al., 2010; He et al., 2016; Van Nostrand et al., 2014; Whittaker et al., 2017). 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 (Belanger et al., 2018; Berube-Simard & Pilon, 2018; Schulz et al., 2014).

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 (Blake & Hudson, 2017). 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 (Blake & Hudson, 2017; Hefner & Fassi, 2017). Further, many CHARGE syndrome patients exhibit clival pathology, such as coronal clefts; this is now considered a useful diagnostic criteria for patients (Mahdi & Whitehead, 2018). 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 (de Geus et al., 2017). 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 (Blake et al., 1998) was first adapted to include supplemental clinical abnormalities (Verloes, 2005). More recently, the diagnostic criteria were updated to incorporate results of molecular testing (Hale et al., 2016a). 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) (Bergman et al., 2011; Janssen et al., 2012). 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 (Bergman et al., 2011). This has resulted in the addition of *CHD7* to NGS gene panels for developmental delay, colobomata, heart defects (Corsten-Janssen et al., 2014), and other congenital malformations (van Ravenswaaij-Arts & Martin, 2017). 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 (van Ravenswaaij-Arts & Martin, 2017).

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" (Janssen et al., 2012). 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 (Janssen et al., 2012), 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 (Pauli et al., 2017).

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 (Moccia et al., 2018). Based on these results, it was suggested that "the phenotypic features of CHARGE syndrome overlap with multiple other rare single-gene syndromes" (Moccia et al., 2018).

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" (Gonçalves et al., 2019).

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" (Qin et al., 2020).

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 (Hartshorne et al., 2011).

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 (de Geus et al., 2017; Trider et al., 2017). 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 (Blake et al., 2011). 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) (Hudson et al., 2017). Testing is recommended in all suspected cases of CHARGE syndrome, especially in patients who partially meet the clinical criteria (Bergman et al., 2011; Hale et al., 2016a; Trider et al., 2017).

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 (Hefner & Fassi, 2017). 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 (Hudson et al., 2017). 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 (Dijk et al., 2019).

VI. 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" (CHARGE Syndrome Foundation, 2024).

The National Organization for Rare Disorders (NORD)

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" (National Organization for Rare Disorders, 2024).

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" (Trider et al., 2017).

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 (Hughes et al., 2014). 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 (Hughes et al., 2014).

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 (de Geus et al., 2017).

Recommendation	References
CHARGE is a clinical diagnosis	(Bergman et al., 2011; Blake et al., 1998; Harris et al., 1997; Issekutz et al., 2005; Verloes, 2005)
***CHD7* testing can confirm uncertain diagnosis in mildly affected patients**	(Bergman et al., 2011)
***CHD7* testing may be performed according to a flow diagram**	(Bergman et al., 2011)
A genome-wide array should be performed in patients with CHARGE syndrome but without a *CHD7* mutation	(Corsten-Janssen et al., 2013)
Clinical genetics consultation is indicated, including options for prenatal diagnosis	(Bergman et al., 2011; Lalani et al., 2012)
Patients diagnosed with hypogonadotropic hypogonadism and anosmia should be screened for clinical features consistent with CHARGE syndrome	(Jongmans et al., 2009)
Olfactory bulb hypoplasia and semicircular canal aplasia should be considered major signs for CHARGE syndrome	(Asakura et al., 2008; Sanlaville et al., 2006)
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	(Jongmans et al., 2008)
***CHD7* analysis should be performed in patients with a 22q11.2 deletion phenotype without *TBX1* haploinsufficiency**	(Corsten-Janssen et al., 2013)
***CHD7* analysis should be performed in patients with Kallmann syndrome who have at least two additional CHARGE features or semicircular canal anomalies**	(Bergman et al., 2012; Costa-Barbosa et al., 2013; Jongmans et al., 2009)
***CHD7* should be included in massive parallel sequencing gene panels for diagnostics in syndromic heart defects**	(Corsten-Janssen et al., 2014)
***CHD7* analysis should not be performed routinely in patients with only atrial septal defect or conotruncal heart defects**	(Corsten-Janssen et al., 2014)
***CHD7* analysis should not be performed in septo-optic dysplasia patients without features of CHARGE**	(Gregory et al., 2013)
MLPA analysis is indicated if no causal *CHD7* is mutation is found	(Wincent et al., 2008; Wincent et al., 2009)

MLPA analysis is not indicated if no *CHD7* mutation is found	(Bergman et al., 2008)

Guidelines for clinical diagnosis have also been published by Hale et al. (2016a), 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 (Blake et al., 2011), 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 (Bergman et al., 2011). 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" (Hale et al., 2016b).

Bergman et al. (2011) asserted that *CHD7* testing can confirm uncertain diagnoses in mildly affected patients. Moreover, a 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 (2024) 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)" (Usman & Sur, 2024).

VII. 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.

VIII. 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.

IX. Evidence-based Scientific References

Asad, Z., Pandey, A., Babu, A., Sun, Y., Shevade, K., Kapoor, S., Ullah, I., Ranjan, S., Scaria, V., Bajpai, R., & Sachidanandan, C. (2016). Rescue of neural crest-derived phenotypes in a zebrafish CHARGE model by Sox10 downregulation. *Hum Mol Genet*, *25*(16), 3539-3554. https://doi.org/10.1093/hmg/ddw198

Asakura, Y., Toyota, Y., Muroya, K., Kurosawa, K., Fujita, K., Aida, N., Kawame, H., Kosaki, K., & Adachi, M. (2008). Endocrine and radiological studies in patients with molecularly confirmed CHARGE syndrome. *J Clin Endocrinol Metab*, *93*(3), 920-924. https://doi.org/10.1210/jc.2007-1419

Bajpai, R., Chen, D. A., Rada-Iglesias, A., Zhang, J., Xiong, Y., Helms, J., Chang, C. P., Zhao, Y., Swigut, T., & Wysocka, J. (2010). CHD7 cooperates with PBAF to control multipotent neural crest formation. *Nature*, *463*(7283), 958-962. https://doi.org/10.1038/nature08733

Belanger, C., Berube-Simard, F. A., Leduc, E., Bernas, G., Campeau, P. M., Lalani, S. R., Martin, D. M., Bielas, S., Moccia, A., Srivastava, A., Silversides, D. W., & Pilon, N. (2018). Dysregulation of cotranscriptional alternative splicing underlies CHARGE syndrome. *Proc Natl Acad Sci U S A*, *115*(4), E620-E629. https://doi.org/10.1073/pnas.1715378115

Bergman, J. E., de Ronde, W., Jongmans, M. C., Wolffenbuttel, B. H., Drop, S. L., Hermus, A., Bocca, G., Hoefsloot, L. H., & van Ravenswaaij-Arts, C. M. (2012). The results of CHD7 analysis in clinically well-characterized patients with Kallmann syndrome. *J Clin Endocrinol Metab*, *97*(5), E858-862. https://doi.org/10.1210/jc.2011-2652

Bergman, J. E., de Wijs, I., Jongmans, M. C., Admiraal, R. J., Hoefsloot, L. H., & van Ravenswaaij-Arts, C. M. (2008). Exon copy number alterations of the CHD7 gene are not a major cause of CHARGE and CHARGE-like syndrome. *Eur J Med Genet*, *51*(5), 417-425. https://doi.org/10.1016/j.ejmg.2008.03.003

Bergman, J. E., Janssen, N., Hoefsloot, L. H., Jongmans, M. C., Hofstra, R. M., & van Ravenswaaij-Arts, C. M. (2011). CHD7 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype. *J Med Genet*, *48*(5), 334-342. https://doi.org/10.1136/jmg.2010.087106

Berube-Simard, F. A., & Pilon, N. (2018). Molecular dissection of CHARGE syndrome highlights the vulnerability of neural crest cells to problems with alternative splicing and other transcription-related processes. *Transcription*, 1-8. https://doi.org/10.1080/21541264.2018.1521213

Bilan, F., Legendre, M., Charraud, V., Maniere, B., Couet, D., Gilbert-Dussardier, B., & Kitzis, A. (2012). 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*, *14*(1), 46-55. https://doi.org/10.1016/j.jmoldx.2011.08.003

Blake, K., van Ravenswaaij-Arts, C. M., Hoefsloot, L., & Verloes, A. (2011). Clinical utility gene card for: CHARGE syndrome. *Eur J Hum Genet*, *19*(9). https://doi.org/10.1038/ejhg.2011.45

Blake, K. D., Davenport, S. L., Hall, B. D., Hefner, M. A., Pagon, R. A., Williams, M. S., Lin, A. E., & Graham, J. M., Jr. (1998). CHARGE association: an update and review for the primary pediatrician. *Clin Pediatr (Phila)*, *37*(3), 159-173. https://doi.org/10.1177/000992289803700302

Blake, K. D., & Hudson, A. S. (2017). Gastrointestinal and feeding difficulties in CHARGE syndrome: A review from head-to-toe. *Am J Med Genet C Semin Med Genet*, *175*(4), 496-506. https://doi.org/10.1002/ajmg.c.31586

CHARGE Syndrome Foundation. (2024). *CHARGE Syndrome Fact Sheet*. CHARGE Syndrome Foundation. https://www.chargesyndrome.org/for-families/new-diagnosis/factsheet/

Corsten-Janssen, N., du Marchie Sarvaas, G. J., Kerstjens-Frederikse, W. S., Hoefsloot, L. H., van Beynum, I. M., Kapusta, L., & van Ravenswaaij-Arts, C. M. (2014). CHD7 mutations are not a major cause of atrioventricular septal and conotruncal heart defects. *Am J Med Genet A*, *164A*(12), 3003-3009. https://doi.org/10.1002/ajmg.a.36747

Corsten-Janssen, N., Saitta, S. C., Hoefsloot, L. H., McDonald-McGinn, D. M., Driscoll, D. A., Derks, R., Dickinson, K. A., Kerstjens-Frederikse, W. S., Emanuel, B. S., Zackai, E. H., & van Ravenswaaij-Arts, C. M. (2013). More Clinical Overlap between 22q11.2 Deletion Syndrome and CHARGE Syndrome than Often Anticipated. *Mol Syndromol*, *4*(5), 235-245. https://doi.org/10.1159/000351127

Costa-Barbosa, F. A., Balasubramanian, R., Keefe, K. W., Shaw, N. D., Al-Tassan, N., Plummer, L., Dwyer, A. A., Buck, C. L., Choi, J. H., Seminara, S. B., Quinton, R., Monies, D., Meyer, B., Hall, J. E., Pitteloud, N., & Crowley, W. F., Jr. (2013). Prioritizing genetic testing in patients with Kallmann syndrome using clinical phenotypes. *J Clin Endocrinol Metab*, *98*(5), E943-953. https://doi.org/10.1210/jc.2012-4116

de Geus, C. M., Free, R. H., Verbist, B. M., Sival, D. A., Blake, K. D., Meiners, L. C., & van Ravenswaaij-Arts, C. M. A. (2017). Guidelines in CHARGE syndrome and the missing link: Cranial imaging. *Am J Med Genet C Semin Med Genet*, *175*(4), 450-464. https://doi.org/10.1002/ajmg.c.31593

Dijk, D. R., Bocca, G., & van Ravenswaaij-Arts, C. M. (2019). Growth in CHARGE syndrome: optimizing care with a multidisciplinary approach. *J Multidiscip Healthc*, *12*, 607-620. https://doi.org/10.2147/jmdh.S175713

Gonçalves, C. I., Patriarca, F. M., Aragüés, J. M., Carvalho, D., Fonseca, F., Martins, S., Marques, O., Pereira, B. D., Martinez-de-Oliveira, J., & Lemos, M. C. (2019). High frequency of CHD7 mutations in congenital hypogonadotropic hypogonadism. *Scientific Reports*, *9*(1), 1597. https://doi.org/10.1038/s41598-018-38178-y

Gregory, L. C., Gevers, E. F., Baker, J., Kasia, T., Chong, K., Josifova, D. J., Caimari, M., Bilan, F., McCabe, M. J., & Dattani, M. T. (2013). Structural pituitary abnormalities associated with CHARGE syndrome. *J Clin Endocrinol Metab*, *98*(4), E737-743. https://doi.org/10.1210/jc.2012-3467

Guercio, J. R., & Martyn, L. J. (2007). Congenital malformations of the eye and orbit. *Otolaryngol Clin North Am*, *40*(1), 113-140, vii. https://doi.org/10.1016/j.otc.2006.11.013

Hale, C. L., Niederriter, A. N., Green, G. E., & Martin, D. M. (2016a). Atypical phenotypes associated with pathogenic CHD7 variants and a proposal for broadening CHARGE syndrome clinical diagnostic criteria. *Am J Med Genet A*, *170A*(2), 344-354. https://doi.org/10.1002/ajmg.a.37435

Hale, C. L., Niederriter, A. N., Green, G. E., & Martin, D. M. (2016b). 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*, *170*(12), 3367-3368. https://doi.org/10.1002/ajmg.a.37629

Hall, B. D. (1979). Choanal atresia and associated multiple anomalies. *J Pediatr*, *95*(3), 395-398. https://www.ncbi.nlm.nih.gov/pubmed/469662

Harris, J., Robert, E., & Kallen, B. (1997). Epidemiology of choanal atresia with special reference to the CHARGE association. *Pediatrics*, *99*(3), 363-367.

Hartshorne, T. S., Stratton, K. K., & van Ravenswaaij-Arts, C. M. (2011). Prevalence of genetic testing in CHARGE syndrome. *J Genet Couns*, *20*(1), 49-57. https://doi.org/10.1007/s10897-010-9328-7

He, D., Marie, C., Zhao, C., Kim, B., Wang, J., Deng, Y., Clavairoly, A., Frah, M., Wang, H., He, X., Hmidan, H., Jones, B. V., Witte, D., Zalc, B., Zhou, X., Choo, D. I., Martin, D. M., Parras, C., & Lu, Q. R. (2016). Chd7 cooperates with Sox10 and regulates the onset of CNS myelination and remyelination. *Nat Neurosci*, *19*(5), 678-689. https://doi.org/10.1038/nn.4258

Hefner, M. A., & Fassi, E. (2017). Genetic counseling in CHARGE syndrome: Diagnostic evaluation through follow up. *Am J Med Genet C Semin Med Genet*, *175*(4), 407-416. https://doi.org/10.1002/ajmg.c.31589

Hittner, H. M., Hirsch, N. J., Kreh, G. M., & Rudolph, A. J. (1979). Colobomatous microphthalmia, heart disease, hearing loss, and mental retardation--a syndrome. *J Pediatr Ophthalmol Strabismus*, *16*(2), 122-128. https://www.ncbi.nlm.nih.gov/pubmed/458518

Hudson, A., Trider, C.-L., & Blake, K. (2017). CHARGE Syndrome. *Pediatrics in Review*, *38*(1), 56-59. https://doi.org/10.1542/pir.2016-0050

Hughes, S. S., Welsh, H. I., Safina, N. P., Bejaoui, K., & Ardinger, H. H. (2014). Family history and clefting as major criteria for CHARGE syndrome. *Am J Med Genet A*, *164a*(1), 48-53. https://doi.org/10.1002/ajmg.a.36192

Isaacson, G. C. (2022, 01/10/2022). *Congenital anomalies of the nose*. UpToDate, Inc. https://www.uptodate.com/contents/congenital-anomalies-of-the-nose

Issekutz, K. A., Graham, J. M., Jr., Prasad, C., Smith, I. M., & Blake, K. D. (2005). An epidemiological analysis of CHARGE syndrome: preliminary results from a Canadian study. *Am J Med Genet A*, *133a*(3), 309-317. https://doi.org/10.1002/ajmg.a.30560

Janssen, N., Bergman, J. E., Swertz, M. A., Tranebjaerg, L., Lodahl, M., Schoots, J., Hofstra, R. M., van Ravenswaaij-Arts, C. M., & Hoefsloot, L. H. (2012). Mutation update on the CHD7 gene involved in CHARGE syndrome. *Hum Mutat*, *33*(8), 1149-1160. https://doi.org/10.1002/humu.22086

Jongmans, M. C., Admiraal, R. J., van der Donk, K. P., Vissers, L. E., Baas, A. F., Kapusta, L., van Hagen, J. M., Donnai, D., de Ravel, T. J., Veltman, J. A., Geurts van Kessel, A., De Vries, B. B., Brunner, H. G., Hoefsloot, L. H., & van Ravenswaaij, C. M. (2006). CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene. *J Med Genet*, *43*(4), 306-314. https://doi.org/10.1136/jmg.2005.036061

Jongmans, M. C., Hoefsloot, L. H., van der Donk, K. P., Admiraal, R. J., Magee, A., van de Laar, I., Hendriks, Y., Verheij, J. B., Walpole, I., Brunner, H. G., & van Ravenswaaij, C. M. (2008). Familial CHARGE syndrome and the CHD7 gene: a recurrent missense mutation, intrafamilial recurrence and variability. *Am J Med Genet A*, *146A*(1), 43-50. https://doi.org/10.1002/ajmg.a.31921

Jongmans, M. C., van Ravenswaaij-Arts, C. M., Pitteloud, N., Ogata, T., Sato, N., Claahsen-van der Grinten, H. L., van der Donk, K., Seminara, S., Bergman, J. E., Brunner, H. G., Crowley, W. F., Jr., & Hoefsloot, L. H. (2009). CHD7 mutations in patients initially diagnosed with Kallmann syndrome--the clinical overlap with CHARGE syndrome. *Clin Genet*, *75*(1), 65-71. https://doi.org/10.1111/j.1399-0004.2008.01107.x

Lalani, S. R., Hefner, M. A., Belmont, J. W., & Davenport, S. L. (2012). CHARGE syndrome In R. A. Pagon, M. P. Adam, & H. H. Ardinger (Eds.), *GeneReviews (R)*. University of Washington, SEattle.

Longman. (2018). *Obstetric Imaging: Fetal Diagnosis and Care*.

Mahdi, E. S., & Whitehead, M. T. (2018). Clival Malformations in CHARGE Syndrome. *AJNR Am J Neuroradiol*, *39*(6), 1153-1156. https://doi.org/10.3174/ajnr.A5612

Marfella, C. G., & Imbalzano, A. N. (2007). The Chd family of chromatin remodelers. *Mutat Res*, *618*(1-2), 30-40. https://doi.org/10.1016/j.mrfmmm.2006.07.012

Moccia, A., Srivastava, A., Skidmore, J. M., Bernat, J. A., Wheeler, M., Chong, J. X., Nickerson, D., Bamshad, M., Hefner, M. A., Martin, D. M., & Bielas, S. L. (2018). Genetic analysis of CHARGE syndrome identifies overlapping molecular biology. *Genet Med*, *20*(9), 1022-1029. https://doi.org/10.1038/gim.2017.233

National Organization for Rare Disorders, I. (2024). *CHARGE Syndrome*. National Organization for Rare Disorders, Inc. https://rarediseases.org/rare-diseases/charge-syndrome/

Pagon, R. A., Graham, J. M., Jr., Zonana, J., & Yong, S. L. (1981). Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr*, *99*(2), 223-227. https://www.ncbi.nlm.nih.gov/pubmed/6166737

Pauli, S., Bajpai, R., & Borchers, A. (2017). CHARGEd with neural crest defects. *Am J Med Genet C Semin Med Genet*, *175*(4), 478-486. https://doi.org/10.1002/ajmg.c.31584

Qin, Z., Su, J., Li, M., Yang, Q., Yi, S., Zheng, H., Zhang, Q., Chen, F., Yi, S., Lu, W., Li, W., Huang, L., Xu, J., Shen, Y., & Luo, J. (2020). Clinical and Genetic Analysis of CHD7 Expands the Genotype and Phenotype of CHARGE Syndrome. *Front Genet*, *11*, 592. https://doi.org/10.3389/fgene.2020.00592

Sanlaville, D., Etchevers, H. C., Gonzales, M., Martinovic, J., Clement-Ziza, M., Delezoide, A. L., Aubry, M. C., Pelet, A., Chemouny, S., Cruaud, C., Audollent, S., Esculpavit, C., Goudefroye, G., Ozilou, C., Fredouille, C., Joye, N., Morichon-Delvallez, N., Dumez, Y., Weissenbach, J., . . . Attie-Bitach, T. (2006). Phenotypic spectrum of CHARGE syndrome in fetuses with CHD7 truncating mutations correlates with expression during human development. *J Med Genet*, *43*(3), 211-217. https://doi.org/10.1136/jmg.2005.036160

Schulz, Y., Wehner, P., Opitz, L., Salinas-Riester, G., Bongers, E. M., van Ravenswaaij-Arts, C. M., Wincent, J., Schoumans, J., Kohlhase, J., Borchers, A., & Pauli, S. (2014). CHD7, the gene mutated in CHARGE syndrome, regulates genes involved in neural crest cell guidance. *Hum Genet*, *133*(8), 997-1009. https://doi.org/10.1007/s00439-014-1444-2

Sperry, E. D., Hurd, E. A., Durham, M. A., Reamer, E. N., Stein, A. B., & Martin, D. M. (2014). The chromatin remodeling protein CHD7, mutated in CHARGE syndrome, is necessary for

proper craniofacial and tracheal development. *Dev Dyn*, *243*(9), 1055-1066. https://doi.org/10.1002/dvdy.24156

Trider, C. L., Arra-Robar, A., van Ravenswaaij-Arts, C., & Blake, K. (2017). Developing a CHARGE syndrome checklist: Health supervision across the lifespan (from head to toe). *Am J Med Genet A*, *173*(3), 684-691. https://doi.org/10.1002/ajmg.a.38085

Usman, N., & Sur, M. (2024). CHARGE Syndrome. In *StatPearls*. https://www.ncbi.nlm.nih.gov/pubmed/32644625

Van Nostrand, J. L., Brady, C. A., Jung, H., Fuentes, D. R., Kozak, M. M., Johnson, T. M., Lin, C. Y., Lin, C. J., Swiderski, D. L., Vogel, H., Bernstein, J. A., Attie-Bitach, T., Chang, C. P., Wysocka, J., Martin, D. M., & Attardi, L. D. (2014). Inappropriate p53 activation during development induces features of CHARGE syndrome. *Nature*, *514*(7521), 228-232. https://doi.org/10.1038/nature13585

van Ravenswaaij-Arts, C., & Martin, D. M. (2017). New insights and advances in CHARGE syndrome: Diagnosis, etiologies, treatments, and research discoveries. *Am J Med Genet C Semin Med Genet*, *175*(4), 397-406. https://doi.org/10.1002/ajmg.c.31592

Verloes, A. (2005). Updated diagnostic criteria for CHARGE syndrome: a proposal. *Am J Med Genet A*, *133A*(3), 306-308. https://doi.org/10.1002/ajmg.a.30559

Vissers, L. E., van Ravenswaaij, C. M., Admiraal, R., Hurst, J. A., de Vries, B. B., Janssen, I. M., van der Vliet, W. A., Huys, E. H., de Jong, P. J., Hamel, B. C., Schoenmakers, E. F., Brunner, H. G., Veltman, J. A., & van Kessel, A. G. (2004). Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nat Genet*, *36*(9), 955-957. https://doi.org/10.1038/ng1407

Whittaker, D. E., Riegman, K. L., Kasah, S., Mohan, C., Yu, T., Sala, B. P., Hebaishi, H., Caruso, A., Marques, A. C., Michetti, C., Smachetti, M. E., Shah, A., Sabbioni, M., Kulhanci, O., Tee, W. W., Reinberg, D., Scattoni, M. L., Volk, H., McGonnell, I., . . . Basson, M. A. (2017). The chromatin remodeling factor CHD7 controls cerebellar development by regulating reelin expression. *J Clin Invest*, *127*(3), 874-887. https://doi.org/10.1172/JCI83408

Wincent, J., Holmberg, E., Stromland, K., Soller, M., Mirzaei, L., Djureinovic, T., Robinson, K., Anderlid, B., & Schoumans, J. (2008). CHD7 mutation spectrum in 28 Swedish patients diagnosed with CHARGE syndrome. *Clin Genet*, *74*(1), 31-38. https://doi.org/10.1111/j.1399-0004.2008.01014.x

Wincent, J., Schulze, A., & Schoumans, J. (2009). Detection of CHD7 deletions by MLPA in CHARGE syndrome patients with a less typical phenotype. *Eur J Med Genet*, *52*(4), 271-272. https://doi.org/10.1016/j.ejmg.2009.02.005

X. Review/Revision History

Effective Date	Summary
04/01/2025	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: CC1, 2, and 3, edited references to mutations to now reflect updated nomenclature, using variants/likely pathogenic/pathogenic variants when discussing germline changes, vs mutations for somatic changes.

	New CC4: “4) For individuals with clinical features of CHARGE syndrome who have already tested negative for likely pathogenic or pathogenic variants in CHD7, screening for variants in ZEB2, KMT2D and EFTUD2 MEETS COVERAGE CRITERIA.” Added CPT code 81403, 81404, 81405, 81479
12/01/2024	Initial Policy Implementation