

Genetic Testing for CHARGE Syndrome

Policy Number: AHS – M2070 – Genetic Testing for CHARGE Syndrome	Prior Policy Name and Number, as applicable:
Initial Policy Effective Date: 12/01/2024	

[POLICY DESCRIPTION](#) | [RELATED POLICIES](#) | [INDICATIONS AND/OR LIMITATIONS OF COVERAGE](#) | [TABLE OF TERMINOLOGY](#) | [SCIENTIFIC BACKGROUND](#) | [GUIDELINES AND RECOMMENDATIONS](#) | [APPLICABLE STATE AND FEDERAL REGULATIONS](#) | [APPLICABLE CPT/HCPCS PROCEDURE CODES](#) | [EVIDENCE-BASED SCIENTIFIC REFERENCES](#) | [REVISION HISTORY](#)

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). 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 *CHD7* **MEETS COVERAGE CRITERIA.**
- 2) For asymptomatic individuals who have a first-degree relative (see Note 1) diagnosed with CHARGE syndrome who have a known mutation, genetic testing restricted to the known familial *CHD7* mutation **MEETS COVERAGE CRITERIA.**
- 3) For individuals seeking prenatal or pre-implantation screening, genetic testing for *CHD7* **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.

- 4) 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
<i>CHD7</i>	<i>Chromodomain helicase deoxyribonucleic acid binding protein 7</i>
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
<i>EFTUD2</i>	<i>Elongation factor Tu GTP binding domain containing 2</i>
ENT	Ear, nose, and throat
<i>EP300</i>	<i>E1A binding protein p300</i>
FDA	Food and Drug Administration
GI	Gastrointestinal
<i>GnRH</i>	<i>Gonadotropin-releasing hormone</i>
HH	Hypogonadotropic hypogonadism
<i>KMT2D</i>	<i>Lysine methyltransferase 2D</i>
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
<i>PUF60</i>	<i>Poly(U) binding splicing factor 60</i>
<i>RERE</i>	<i>Arginine-glutamic acid dipeptide repeats</i>
SNP	Single nucleotide polymorphism

SWI-SNF	Switch/sucrose non-fermentable
<i>TBX1</i>	<i>T-box transcription factor 1</i>
<i>ZEB2</i>	<i>Zinc finger E-box binding homeobox 2</i>

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, 2022).

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, 2023).

The National Organization for Rare Disorders (NORD)

NORD states that “molecular genetic testing is available for mutations in the *CHD7* gene associated with the condition, and if this is negative, a SNP chromosomal microarray should be done, because in a few cases, there has been a submicroscopic genomic alteration of chromosome 8q12.2. 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 de novo mutations in *ZEB2*, *KMT2D* and *EFTUD2* have been detected in children previously diagnosed as having CHARGE syndrome” (National Organization for Rare Disorders, 2021).

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)
<i>CHD7</i> testing can confirm uncertain diagnosis in mildly affected patients	(Bergman et al., 2011)
<i>CHD7</i> 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 <i>CHD7</i> 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 <i>CHD7</i> pathogenic variant has been identified in the proband	(Jongmans et al., 2008)
<i>CHD7</i> analysis should be performed in patients with a 22q11.2 deletion phenotype without <i>TBX1</i> haploinsufficiency	(Corsten-Janssen et al., 2013)
<i>CHD7</i> 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)
<i>CHD7</i> should be included in massive parallel sequencing gene panels for diagnostics in syndromic heart defects	(Corsten-Janssen et al., 2014)
<i>CHD7</i> analysis should not be performed routinely in patients with only atrial septal defect or conotruncal heart defects	(Corsten-Janssen et al., 2014)
<i>CHD7</i> 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 <i>CHD7</i> mutation is found	(Wincent et al., 2008; Wincent et al., 2009)
MLPA analysis is not indicated if no <i>CHD7</i> 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 (2022) compiled guidelines for the diagnosis of CHARGE syndrome that state “the sequencing of *CHD7* encoding the chromodomain helicase DNA binding protein 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 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, 2022).

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
81407	Molecular pathology procedure, level 8 Gene: CHD7 (chromodomain helicase DNA binding protein 7, full gene sequence)

Current Procedural Terminology© American Medical Association. All Rights reserved.

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. (2023). *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. (2021). *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). CHARGEEd 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. (2022). 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>

Visser, 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
12/01/2024	Initial Policy Implementation