BlueCross BlueShield of North Carolina

An independent licensee of the Blue Cross and Blue Shield Association

Corporate Medical Policy

Genetic Testing for CHARGE Syndrome AHS – M2070

File Name:	genetic_testing_for_charge_syndrome
Origination:	01/01/2019
Last CAP Review:	07/2020
Next CAP Review:	07/2021
Last Review:	01/2021

Description of Procedure or Service

CHARGE syndrome is an autosomal dominant genetic disease caused by mutations of the chromodomain helicase DNA binding protein 7 gene (*CHD7*) gene on chromosome 8q12.1 (Vissers et al., 2004) resulting in a wide range of congenital anomalies, including colobomas, which is a congenital absence of pieces of tissue in eye structures that may cause defects in the iris, retina, or optic nerve; heart defects; choanal atresia, which is 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, 2018; Jongmans et al., 2006).

Related Policies
General Genetic Testing, Germline Disorders AHS – M2145

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for genetic testing for CHARGE syndrome when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for CHARGE Syndrome is covered

Genetic testing for CHARGE syndrome is considered medically necessary to confirm a diagnosis in a patient with signs/symptoms of CHARGE syndrome when a definitive diagnosis cannot be made with clinical criteria.

Genetic testing for known familial variant mutations of CHARGE syndrome in first degree relatives of an affected individual is considered medically necessary.

Mutation testing for CHARGE syndrome in cases of prenatal testing and preimplantation is considered medically necessary.

When Genetic Testing for CHARGE Syndrome is not covered

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

Policy Guidelines

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, Hirsch, Kreh, and Rudolph (1979), CHARGE syndrome was diagnosed clinically (K. D. Blake et al., 1998; Pagon, Graham, Zonana, & Yong, 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 great 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).

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). The *CHD7* gene contains 38 exons that encode for the 300-kDa CHD7 chromatin remodeler protein (Bilan et al., 2012). It has an important, dosage-dependent role in the development of several different 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 be responsible for additional sensory deficits and birth defects, including cranial nerve dysfunction, clival pathology, and feeding and gastrointestinal (GI) dysfunction (K. D. Blake & Hudson, 2017). More than 90% of patients experience feeding and GI dysfunction; this is known to cause a great amount of morbidity and mortality in the CHARGE syndrome patient population (K. D. 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 malady for patients (Mahdi & Whitehead, 2018). Nonetheless, the wide range of gene expression affected by 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 (K. D. 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, Niederriter, Green, & Martin, 2016). The majority of 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 (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 of CHARGE syndrome, 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).

The cause of CHARGE syndrome remains unclear in approximately 5-10% of cases which may be due to variants, such as whole gene deletions, that are not detectable in currently used assays (Janssen et al., 2012). Other genes or genetic conditions may also be involved in CHARGE syndrome, such as 22q11.2 deletion (DiGeorge) syndrome, Kallmann syndrome, and Kabuki syndrome; these conditions are known to have an overlapping phenotypic spectrum with CHARGE syndrome (Janssen et al., 2012). 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, Bajpai, & Borchers, 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 mutations, 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 the *CHD7* mutation (Hartshorne, Stratton, & van Ravenswaaij-Arts, 2011).

Clinical Utility

Patients with CHARGE syndrome experience a wide spectrum of comorbidities, some more severe than others and the complex management of these comorbidities oftentimes can 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, Arra-Robar, van Ravenswaaij-Arts, & Blake, 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 (K. Blake, van Ravenswaaij-Arts, Hoefsloot, & Verloes, 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, Trider, & Blake, 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., 2016; 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, proving a high clinical utility of *CHD7* testing of CHARGE syndrome (Dijk, Bocca, & van Ravenswaaij-Arts, 2019).

Guidelines and Recommendations

To date, no formal professional society guidelines or recommendations have been found regarding the genetic testing of CHARGE syndrome patients. Therefore, recommendations by subject matter experts in the field are included below.

A comprehensive guideline and clinical checklist was 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 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 may be passed down genetically, showing that family history should be considered as a major diagnostic criterion for CHARGE syndrome (Hughes, Welsh, Safina, Bejaoui, & Ardinger, 2014). Moreover, orofacial clefting is often seen 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 regarding genetics of CHARGE is in the table below (de Geus et al., 2017).

Recommendation	References

CHARGE is a clinical diagnosis	(Bergman et al., 2011; K. D. Blake et al., 1998; Harris, Robert, & Kallen, 1997; Issekutz, Graham, Prasad, Smith, & Blake, 2005; Verloes, 2005)
CHD7 testing can confirm uncertain diagnosis in mildly affected patients	(Bergman et al., 2011)
CHD7 testing may be performed according to 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, Hefner, Belmont, & Davenport, 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 conotrunctal heart defects	(Corsten-Janssen et al., 2014)
CHD7 analysis should not be performed in septo-optic dysplasia without features of CHARGE	(Gregory et al., 2013)
MLPA analysis is indicated if no causal *CHD7* is mutation found	(Wincent et al., 2008; Wincent, Schulze, & Schoumans, 2009)
MLPA analysis not indicated if no *CHD7*mutation found	(Bergman et al., 2008)

Guidelines for clinical diagnosis have most recently been published by Hale (2016) which include identification of a pathogenic CHD7 variant as major criteria for diagnosis of CHARGE syndrome.

Bergman et al. (2011) published recommendations which stated that *CHD7* testing can confirm uncertain diagnoses in mildly affected patients; a clinical genetics consultation is also indicated, including options for prenatal diagnosis.

Corsten-Janssen et al (2014) published recommendations which state the following:

- 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; 2009) recommended the following:

- 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 (2020) compiled guidelines for evaluation that were rooted in temporal bone imaging and clinical findings, and they ultimately concluded that evaluation via prenatal genetic screenings of CHD7 variants was only restricted to familial cases via amniocentesis or chorionic villus screening at 10-12 and 18-20 weeks' gestation, respectively.

Applicable Federal Regulations

A total of 24 U.S. Food and Drug Administration-cleared tests were found with the keyword "genotyping" as of 8/30/2020. Additionally, 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 have not been approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81407

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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

Asakura, Y., Toyota, Y., Muroya, K., Kurosawa, K., Fujita, K., Aida, N., . . . Adachi, M. (2008). Endocrine and radiological studies in patients with molecularly confirmed CHARGE syndrome. *J Clin Endocrinol Metab, 93*(3), 920-924. doi:10.1210/jc.2007-1419
Bajpai, R., Chen, D. A., Rada-Iglesias, A., Zhang, J., Xiong, Y., Helms, J., . . . Wysocka, J. (2010). CHD7 cooperates with PBAF to control multipotent neural crest formation. *Nature, 463*(7283), 958-962. doi:10.1038/nature08733
Belanger, C., Berube-Simard, F. A., Leduc, E., Bernas, G., Campeau, P. M., Lalani, S. R., . . . Pilon, N. (2018). Dysregulation of cotranscriptional alternative splicing underlies CHARGE syndrome. *Proc Natl Acad Sci U S A, 115*(4), E620-E629. doi:10.1073/pnas.1715378115
Bergman, J. E., de Ronde, W., Jongmans, M. C., Wolffenbuttel, B. H., Drop, S. L., Hermus, A., . . . 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. doi: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. doi: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. doi: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. doi: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. doi: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). doi:10.1038/ejhg.2011.45
Blake, K. D., Davenport, S. L., Hall, B. D., Hefner, M. A., Pagon, R. A., Williams, M. S., . . . Graham, J. M., Jr. (1998). CHARGE association: an update and review for the primary pediatrician. *Clin Pediatr (Phila), 37*(3), 159-173. doi: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. doi:10.1002/ajmg.c.31586
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. doi:10.1002/ajmg.a.36747
Corsten-Janssen, N., Saitta, S. C., Hoefsloot, L. H., McDonald-McGinn, D. M., Driscoll, D. A., Derks, R., . . . 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. doi:10.1159/000351127
Costa-Barbosa, F. A., Balasubramanian, R., Keefe, K. W., Shaw, N. D., Al-Tassan, N., Plummer, L., . . . Crowley, W. F., Jr. (2013). Prioritizing genetic testing in patients with Kallmann syndrome using clinical phenotypes. *J Clin Endocrinol Metab, 98*(5), E943-953. doi: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. doi: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. doi:10.2147/jmdh.S175713
Gonçalves, C. I., Patriarca, F. M., Aragüés, J. M., Carvalho, D., Fonseca, F., Martins, S., . . . Lemos, M. C. (2019). High frequency of CHD7 mutations in congenital hypogonadotropic hypogonadism. *Scientific Reports, 9*(1), 1597. doi:10.1038/s41598-018-38178-y

Gregory, L. C., Gevers, E. F., Baker, J., Kasia, T., Chong, K., Josifova, D. J., . . . Dattani, M. T. (2013). Structural pituitary abnormalities associated with CHARGE syndrome. *J Clin Endocrinol Metab, 98*(4), E737-743. doi: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. doi:10.1016/j.otc.2006.11.013
Hale, C. L., Niederriter, A. N., Green, G. E., & Martin, D. M. (2016). 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. doi:10.1002/ajmg.a.37435
Hall, B. D. (1979). Choanal atresia and associated multiple anomalies. *J Pediatr, 95*(3), 395-398. Retrieved from 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. doi:10.1007/s10897-010-9328-7
He, D., Marie, C., Zhao, C., Kim, B., Wang, J., Deng, Y., . . . Lu, Q. R. (2016). Chd7 cooperates with Sox10 and regulates the onset of CNS myelination and remyelination. *Nat Neurosci, 19*(5), 678-689. doi: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. doi: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. Retrieved from 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. doi: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. doi:10.1002/ajmg.a.36192
Isaacson, G. C. (2018). Congenital anomalies of the nose. Retrieved from https://www.uptodate.com/contents/congenital-anomalies-of-the-nose#H10
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. doi:10.1002/ajmg.a.30560
Janssen, N., Bergman, J. E., Swertz, M. A., Tranebjaerg, L., Lodahl, M., Schoots, J., . . . Hoefsloot, L. H. (2012). Mutation update on the CHD7 gene involved in CHARGE syndrome. *Hum Mutat, 33*(8), 1149-1160. doi:10.1002/humu.22086
Jongmans, M. C., Admiraal, R. J., van der Donk, K. P., Vissers, L. E., Baas, A. F., Kapusta, L., . . . van Ravenswaaij, C. M. (2006). CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene. *J Med Genet, 43*(4), 306-314. doi: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., . . . 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. doi: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., . . . 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. doi: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)*. Seattle: 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. doi:10.3174/ajnr.A5612
Marfella, C. G., & Imbalzano, A. N. (2007). The Chd family of chromatin remodelers. *Mutat Res, 618*(1-2), 30-40. doi:10.1016/j.mrfmmm.2006.07.012
Moccia, A., Srivastava, A., Skidmore, J. M., Bernat, J. A., Wheeler, M., Chong, J. X., . . . Bielas, S. L. (2018). Genetic analysis of CHARGE syndrome identifies overlapping molecular biology. *Genet Med, 20*(9), 1022-1029. doi:10.1038/gim.2017.233

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. Retrieved from 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. doi:10.1002/ajmg.c.31584
Qin, Z., Su, J., Li, M., Yang, Q., Yi, S., Zheng, H., . . . Luo, J. (2020). Clinical and Genetic Analysis of CHD7 Expands the Genotype and Phenotype of CHARGE Syndrome. *Front Genet, 11*, 592. doi:10.3389/fgene.2020.00592
Sanlaville, D., Etchevers, H. C., Gonzales, M., Martinovic, J., Clement-Ziza, M., Delezoide, A. L., . . . 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. doi:10.1136/jmg.2005.036160
Schulz, Y., Wehner, P., Opitz, L., Salinas-Riester, G., Bongers, E. M., van Ravenswaaij-Arts, C. M., . . . Pauli, S. (2014). CHD7, the gene mutated in CHARGE syndrome, regulates genes involved in neural crest cell guidance. *Hum Genet, 133*(8), 997-1009. doi: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. doi: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. doi:10.1002/ajmg.a.38085
Usman, N., & Sur, M. (2020). CHARGE Syndrome. In *StatPearls*. Treasure Island (FL): StatPearls Publishing
Copyright © 2020, StatPearls Publishing LLC.
Van Nostrand, J. L., Brady, C. A., Jung, H., Fuentes, D. R., Kozak, M. M., Johnson, T. M., . . . Attardi, L. D. (2014). Inappropriate p53 activation during development induces features of CHARGE syndrome. *Nature, 514*(7521), 228-232. doi: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. doi: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. doi: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 Kessel, A. G. (2004). Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nat Genet, 36*(9), 955-957. doi:10.1038/ng1407
Whittaker, D. E., Riegman, K. L., Kasah, S., Mohan, C., Yu, T., Sala, B. P., . . . Basson, M. A. (2017). The chromatin remodeling factor CHD7 controls cerebellar development by regulating reelin expression. *J Clin Invest, 127*(3), 874-887. doi:10.1172/JCI83408
Wincent, J., Holmberg, E., Stromland, K., Soller, M., Mirzaei, L., Djureinovic, T., . . . Schoumans, J. (2008). CHD7 mutation spectrum in 28 Swedish patients diagnosed with CHARGE syndrome. *Clin Genet, 74*(1), 31-38. doi: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. doi:10.1016/j.ejmg.2009.02.005

Policy Implementation/Update Information

1/1/2019 New policy developed. BCBSNC will provide coverage for genetic testing for CHARGE syndrome when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

4/1/2019 Description section updated. Two additional medically necessary indications added to the When Covered section referring to genetic testing for known familial variant mutations in first degree relatives of an affected individual and mutation testing in cases of prenatal testing and preimplantation testing for CHARGE syndrome. Policy guidelines extensively revised. No change to policy intent. References updated. Medical Director review 4/2019. (jd)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medically Necessity to Reimbursement language, where needed. (hb)

2/11/20 Annual review by Avalon 4th Quarter 2019 CAB. No revisions and no change to policy intent. Medical Director review 12/2019. (jd)

7/28/20 Specialty Matched Consultant Advisory Panel review 7/2020. Medical Director review 7/2020. (jd)

2/9/21 Annual review by Avalon 4th Quarter 2020 CAB. Minor update to policy guidelines; no change to policy intent. Medical Director review 1/2021. (jd)