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Corporate Medical Policy

Genetic Testing for CHARGE Syndrome AHS – M2070

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Description of Procedure or Service

CHARGE (Coloboma, Heart defects, Atresia choanae, Growth retardation, Genital abnormalities, and Ear abnormalities) syndrome is an autosomal dominant genetic disease caused by mutations of the chromodomain helicase DNA binding protein 7 gene (*CHD7*) on chromosome 8q12.1 (Vissers et al., 2004). 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, 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 (Coloboma, Heart defects, Atresia choanae, Growth retardation, Genital abnormalities, and Ear abnormalities) 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.

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

When Genetic Testing for CHARGE Syndrome is not covered

Genetic 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 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, 2020).

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

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).

Guidelines and Recommendations

The CHARGE Syndrome Foundation

The CHARGE Syndrome Foundation states that "diagnosis should be made by a Medical Geneticist. Diagnosis is based on key features, ideally with DNA testing for CHD7 mutations." (The CHARGE Syndrome Foundation, n.d.).

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." (NORD, n.d.).

Other guidelines by professional societies and organizations about genetic testing for CHARGE syndrome have not been found; therefore, 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 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 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. (2016), Hale and colleagues reaffirm 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) 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 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 (2020) compiled guidelines for the diagnosis of CHARGE syndrome that were based on a previous evaluation by van Ravenswaaij-Arts & Martin (2017) that state "Current standard prenatal screening for CHD7 variants is typically limited to familial cases, most often via chorionic villus sampling or amniocentesis at 10–12 and 18–20 weeks' gestation, respectively."

Applicable Federal Regulations

A total of 151 U.S. Food and Drug Administration-cleared or approved human genetic tests were found in the FDA database as of 10/18/2021. 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

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Specialty Matched Consultant Advisory Panel review 7/2020

Medical Director review 7/2020

Specialty Matched Consultant Advisory Panel review 7/2021

Medical Director review 7/2021

Medical Director review 1/2022

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)
9/7/21	Specialty Matched Consultant Advisory Panel review 7/2021. Medical Director review 7/2021. (jd)
2/8/22	Reviewed by Avalon 4th Quarter 2021 CAB. Under the When Covered section, added the following to item #1 for clarity: "(Coloboma, Heart defects, Atresia choanae, Growth retardation, Genital abnormalities, and Ear abnormalities)". Replaced the word "mutation" with "genetic" for clarity in both When Covered and When Not Covered sections. No change to policy intent. Description, policy guidelines, and references updated with minor revisions. Medical Director review 1/2022. (jd)