Corporate Medical Policy

Genetic Testing for CHARGE Syndrome AHS – M2070

File Name: genetic_testing_for_charge_syndrome
Origination: 01/01/2019
Last CAP Review: N/A
Next CAP Review: 07/2020
Last Review: 12/2019

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 coloboma, heart defects, choanal atresia, retarded growth and development, genital hypoplasia, ear anomalies, and deafness (Jongmans et al., 2006).

***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.
Genetic Testing for CHARGE Syndrome AHS – M2070

Policy Guidelines

Background

CHARGE syndrome is a relatively common cause of congenital anomalies affecting approximately 1 in 12,000 births (Kallen, Robert, Mastroiacovo, Castilla, & Kallen, 1999). First described by Hall (1979) and Hittner et al (1979), CHARGE syndrome (Pagon, Graham, Zonana, & Yong, 1981) was diagnosed clinically (K.D. Blake et al., 1998) until the identification of causative mutations in CHD7 in patients with CHARGE syndrome (Vissers et al., 2004).

CHD7 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 development of several different craniofacial tissues (Sperry et al., 2014) and in orchestrating neural crest (Bajpai et al., 2010; Van Nostrand et al., 2014), CNS (He et al., 2016; Whittaker et al., 2017), and other gene expression programs and interactions with other cells during embryogenesis (Schulz et al., 2014), possibly through dysregulation of cotranscriptional alternative splicing (Belanger et al., 2018; Berube-Simard & Pilon, 2018).

The wide range of gene expression affected by mutations in the CHD7 gene result in a broad phenotype that can involve almost all organ and sensory systems, along with significant variability in severity and comorbidity (de Geus et al., 2017) with no single feature universally present or sufficient for the clinical diagnosis of CHARGE syndrome. The initial clinical criteria (K.D. Blake et al., 1998) were adapted to include additional clinical abnormalities (Verloes, 2005) and more recently to include results of molecular testing (Hale, Niederriter, Green, & Martin, 2016).

Clinical Validity

The majority of individuals (90-95%) fulfilling the clinical criteria 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 which would not meet the clinical criteria (Bergman et al., 2011) resulting in CHD7 being added to next generation sequencing (NGS) gene panels for developmental delay, colobomata, heart defects (Corsten-Janssen et al., 2014), and other congenital malformations (van Ravenswaaij-Arts & Martin, 2017).

The cause of CHARGE remains unclear in 5-10% of cases which may be due to variants that are not detectable in currently used assays such as whole gene deletions, other genes possibly involved in CHARGE, or other genetic conditions, such as 22q11.2 deletion syndrome, Kallmann syndrome, and Kabuki syndrome, which have an overlapping phenotypic spectrum with CHARGE syndrome (Janssen et al., 2012).

Clinical Utility

Patients with CHARGE syndrome experience a wide spectrum of comorbidities, some severe and management considerations are often complex. The clinical utility of making a definite diagnosis of CHARGE syndrome is high, in that confirming a diagnosis in a patient will lead to changes in clinical management, including clinical assessment and treatment recommendations that are well defined (de Geus et al., 2017; Trider, Arra-Robar, van Ravenswaaij-Arts, & Blake, 2017). There is no consensus on utility of genetic testing in patients which present with a clear clinical diagnosis, 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). Testing is recommended in all
suspected cases of CHARGE syndrome especially patients who partially meet the clinical criteria (Bergman et al., 2011; Hale et al., 2016; Trider et al., 2017).

Applicable Federal Regulations

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found.

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

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).

As an LDT, the U.S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

Practice Guidelines and Position Statements

A comprehensive guideline and clinical checklist was developed by Trider et al (2017) which includes clinical diagnosis and genetic testing with genetics consultation for CHD7 analysis and array CGH.

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. They summarize their recommendations regarding genetics of CHARGE in the Table below (de Geus et al., 2017):

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARGE is a clinical diagnosis</td>
<td>(Bergman et al., 2011; K. D. Blake et al., 1998; Harris, Robert, &amp; Kallen, 1997; Issekutz, Graham, Prasad, Smith, &amp; Blake, 2005; Verloes, 2005)</td>
</tr>
<tr>
<td>CHD7 testing can confirm uncertain diagnosis in mildly affected patients</td>
<td>(Bergman et al., 2011)</td>
</tr>
<tr>
<td>CHD7 testing may be performed according to flow diagram</td>
<td>(Bergman et al., 2011)</td>
</tr>
<tr>
<td>A genome-wide array should be performed in patients with CHARGE syndrome but without a CHD7 mutation</td>
<td>(Corsten-Janssen et al., 2013)</td>
</tr>
<tr>
<td>Clinical genetics consultation is indicated, including options for prenatal diagnosis</td>
<td>(Bergman et al., 2011; Lalani, Hefner, Belmont, &amp; Davenport, 2012)</td>
</tr>
<tr>
<td>Patients diagnosed with hypogonadotropic hypogonadism and anosmia should be screened for clinical features consistent with CHARGE syndrome</td>
<td>(Jongmans et al., 2009)</td>
</tr>
<tr>
<td>Olfactory bulb hypoplasia and semicircular canal aplasia should be considered major signs for CHARGE syndrome</td>
<td>(Asakura et al., 2008; Sanlaville et al., 2006)</td>
</tr>
</tbody>
</table>
If a parent has any features of CHARGE syndrome, molecular genetic testing is appropriate if a CHD7 pathogenic variant has been identified in the proband (Jongmans et al., 2008)

| CHD7 analysis should be performed in patients with a 22q11.2 deletion phenotype without TBX1 haploinsufficiency | (Corsten-Janssen et al., 2013) |
| CHD7 analysis should be performed in patients with Kallmann syndrome who have at least two additional CHARGE features or semicircular canal anomalies | (Bergman et al., 2012; Costa-Barbosa et al., 2013; Jongmans et al., 2009) |
| CHD7 should be included in massive parallel sequencing gene panels for diagnostics in syndromic heart defects | (Corsten-Janssen et al., 2014) |
| CHD7 analysis should not be performed routinely in patients with only atrial septal defect or conotruncal heart defects | (Corsten-Janssen et al., 2014) |
| CHD7 analysis should not be performed in septo-optic dysplasia without features of CHARGE | (Gregory et al., 2013) |
| MLPA analysis is indicated if no causal CHD7 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 diagnosis in mildly affected patients and that clinical genetics consultation is 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.
**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**


**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1/2019</td>
<td>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)</td>
</tr>
<tr>
<td>4/1/2019</td>
<td>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)</td>
</tr>
<tr>
<td>10/29/19</td>
<td>Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medically Necessity to Reimbursement language, where needed. (hb)</td>
</tr>
<tr>
<td>2/11/20</td>
<td>Annual review by Avalon 4th Quarter 2019 CAB. No revisions and no change to policy intent. Medical Director review 12/2019. (jd)</td>
</tr>
</tbody>
</table>

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.