Genetic Testing for CHARGE Syndrome

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I. Policy Description

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. 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.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request

1) Genetic testing for CHARGE (Coloboma, Heart defects, Atresia choanae, Growth retardation, Genital abnormalities, and Ear abnormalities) syndrome **MEETS COVERAGE CRITERIA** to confirm a diagnosis in a patient with signs/symptoms of CHARGE syndrome when a definitive diagnosis cannot be made with clinical criteria.

2) Genetic testing for known familial variant mutations of CHARGE syndrome in first-degree relatives of an affected individual **MEETS COVERAGE CRITERIA**.

3) Genetic testing for CHARGE syndrome in cases of prenatal testing and pre-implantation **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 a patient's illness.

4) Genetic testing for CHARGE syndrome **DOES NOT MEET COVERAGE CRITERIA** in all other situations.

III. 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. First described by Hall (1979) and Hittner et al. (1979), CHARGE syndrome was diagnosed clinically until causative mutations were identified in the *CHD7* (Chromodomain-helicase-DNA-binding protein 7/ATP-dependent helicase CHD7) gene. Due to the variability associated with *CHD7* mutations, genetic analysis may be helpful for genotypic diagnostics but will not necessarily assist in

phenotypic predictions. 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.

The *CHD7* gene contains 38 exons that encode for the 300-kDa CHD7 chromatin remodeler protein. The CHD7 protein is a member of the SWI-SNF superfamily of ATP-dependent chromatin remodelers that bind to DNA and modulate gene expression. 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. 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.

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. 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. Further, many CHARGE syndrome patients exhibit clival pathology, such as coronal clefts; this is now considered a useful diagnostic criteria for patients. 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. 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 was first adapted to include supplemental clinical abnormalities (Verloes, 2005). More recently, the diagnostic criteria were updated to incorporate results of molecular testing. 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). 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, 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.

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, 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.

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

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."

A study conducted by Qin et al. (2020) also found 5 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 3 novel genetic variants (c.2828_2829delAG, c.4667dupC, and c.7873C > *T*) and 2 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."

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.

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. 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. For instance, many patients with CHARGE syndrome will often have more than 1 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). Testing is recommended in all suspected cases of CHARGE syndrome, especially in patients who partially meet the clinical criteria.

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. 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. 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.

IV. 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 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."

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."

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. 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.

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.

Recommendation	References

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

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

Guidelines for clinical diagnosis have also been published by Hale et al. (2016a), which include the identification of a pathogenic *CHD7* variant as major criteria for a CHARGE syndrome diagnosis. In a response to comments received on their publication by Blake et al. (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. 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."

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."

V. State and Federal Regulations, as applicable

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.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), or for QUEST Integration members under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VII. Evidence-based Scientific References

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VIII. Policy History

Policy approved by Medical Directors	9/20/2022
Policy approved at UMC	12/16/2022
Policy effective	6/1/2023
Updated Lines of Business	12/18/2023