



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Genetic Testing for Congenital, Profound Deafness**

**Effective Date ..... 12/15/2010**  
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**Coverage Policy Number ..... 0254**

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## Hyperlink to Related Coverage Policies

- Aural Rehabilitation
- Cochlear and Auditory Brainstem Implants
- Comparative Genomic Hybridization Testing (Chromosomal Microarray Analysis)
- Genetic Counseling
- Genetic Testing of Heritable Disorders
- Hearing Aids
- Neonatal Auditory Screening

## INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

**CIGNA covers genetic testing for congenital, nonsyndromic, sensorineural, mild-to-profound deafness (DFNB1) as medically necessary for ANY of the following indications:**

- diagnostic testing in an individual with prelingual, nonprogressive, mild-to-profound bilateral hearing loss to identify deafness-causing mutations in the GJB2 gene and/or GJB6 gene
- preconception or prenatal genetic testing to determine carrier status of a prospective biologic parent with the capacity and desire to reproduce in EITHER of the following situations:
  - when the individual has a first- or second-degree relative\* with gene GJB2 or GJB6 mutation
  - when the individual is the reproductive partner of a known carrier (deafness-causing mutation of gene GJB2 or GJB6)
- prenatal testing of a fetus (i.e., amniocentesis or chorionic villus sampling [CVS]) or preimplantation genetic diagnosis (PGD) when both parents are known carriers of deafness-causing mutation of gene GJB2 or GJB6

\*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes. First-degree relatives include the individual's parents, full siblings and children.

\*A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.

**CIGNA does not cover genetic screening for congenital, nonsyndromic, sensorineural, mild-to-profound deafness (DFNB1) in the general population because such screening is considered not medically necessary or of unproven benefit.**

**All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a physician or licensed or certified genetic counselor.**

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## **General Background**

More than 50% of prelingual deafness is genetic, with most of these cases being autosomal recessive and nonsyndromic. Cytomegalovirus (CMV) is one of the most common causes of congenital, nonhereditary hearing loss. Other causes of congenital severe-to-profound hearing loss that may be considered in children who are single cases in their family include: prematurity, low birth weight, low Apgar scores, infection and any illness requiring care in a neonatal intensive care unit. It has been noted that the reduction in the incidence of acquired causes of hearing loss has resulted in hereditary hearing loss accounting for a greater proportion of hearing loss in the general population (Hone and Smith, 2003). More than 70% of hereditary hearing loss is nonsyndromic, with the remaining cases caused by specific genetic syndromes. Hearing loss may be classified in several ways (Smith and Van Camp, 2008):

- Onset:
  - Prelingual: Hearing loss that is present before speech develops. Congenital hearing loss is prelingual; however, not all prelingual hearing loss is congenital.
  - Postlingual: Hearing loss that occurs after the development of normal speech, or late onset.
- Type:
  - Conductive: Hearing loss that results from abnormalities of the external ear and/or the ossicles of middle ear.
  - Sensorineural: Hearing loss that results from malfunction of inner ear structures (i.e., cochlea).
  - Combination or mixed: Hearing loss may also result from a combination of both conductive and sensorineural causes.
- Association with other signs and symptoms:
  - Syndromic: Hearing impairment that is associated with malformations of external ear or other organs or with medical problems that involve other organ systems.
  - Nonsyndromic: Hearing impairment that has no association with visible abnormalities of external ear, nor any related medical problems. It can be associated with abnormalities of middle ear and/or inner ear.

Genetic forms are diagnosed by otologic, audiological, ancillary (i.e., computed tomography [CT] examination of the temporal bone), and DNA-based testing, as well as by physical examination and family history.

Different chromosome sites of nonsyndromic forms of genetic deafness are named under the acronym DFN (from the English word deafness) followed by letters A or B, meaning autosomal dominant transmission (DFNA) and recessive transmission (DFNB), respectively. When using DFN isolated, it is X-linked deafness. After the letters, there is a whole number, indicating the order of gene discovery. DFNB1 is characterized by prelingual, nonprogressive, bilateral hearing loss, which varies from mild to profound, with severe and profound hearing loss the most common. All frequencies may be affected or just the higher ones. Individuals with DFNB1 have normal vestibular function and no radiographic abnormalities of the inner ear or other associated medical findings. In children with DFNB1 related deafness, no cognitive dysfunction is reported, and neural structures are preserved. An interfamilial variability in the degree of deafness may occur. Infants and children with this condition learn to sit and walk at age-appropriate times. Other than the deafness, affected individuals are healthy. Management of DFNB1 may include fitting with hearing aids and enrollment in appropriate educational programs. Cochlear implantation may be considered with severe-to-profound hearing loss.

Mutations of gene GJB2 and deletions involving gene GJB6 are both associated with deafness at the DFNB1 locus. The diagnosis of DFNB1 is made with molecular genetic testing to identify the deafness-causing mutations in GJB2 gene and/or GJB6 gene (Smith and Van Camp, 2008). Approximately 98% of individuals with

DFNB1 have two identifiable GJB2 mutations. Approximately 2% of individuals with DFNB1 have one identifiable GJB2 mutation and one of two large deletions that include a portion of GJB6.

DFNB1 is inherited in an autosomal recessive manner. In each pregnancy, the parents of a proband have a 25% chance of having a deaf child, a 50% chance of having a hearing child who is a carrier, and a 25% chance of having a child who is not a carrier. When the deafness-causing mutation has been detected in one family member, then carrier testing for at-risk family members and prenatal testing for at-risk pregnancies is possible (Smith and Van Camp, 2008).

DFNB1 caused by mutations in GJB2, which encodes the protein connexin 26 (Cx26), and the GJB6 gene, which encodes protein connexin 30 (Cx30), together account for 50% of autosomal recessive nonsyndromic hearing loss. Mutations in GJB2 cause deafness by altering the function of the encoded protein Cx26 within the inner ear. Mutation in GJB2 affects the function of Cx26 and, therefore, is thought to cause aberrancies in potassium circulation, which leads to cell death and deafness (Smith and Hone, 2003). It has been noted that mutations in most of the other DFNB genes have so far been detected in only a small number of families, and their contribution to deafness is thought to be limited (Petersen and Willems, 2006).

The carrier rate in the general population for recessive deafness-causing GJB6 mutation is approximately one in 33. A small percentage of prelingual deafness is due to syndromic or autosomal dominant nonsyndromic cause (Smith and Van Camp, 2008). Mutations in the GJB2 gene are also responsible for syndromic forms of deafness.

Genetic counseling and risk assessment depend on accurate determination of the specific genetic diagnosis. Molecular genetic testing may be used for diagnostic testing, carrier testing and prenatal diagnosis. Carrier testing is generally performed to assist in family planning. Genetic testing used in the diagnosis of congenital, nonsyndromic hearing loss may provide several benefits, including (Robin, et al., 2005):

- avoiding medically unnecessary and costly testing
- allowing accurate recurrence risk counseling
- dispelling incorrect notion of the cause of the hearing impairment
- offer limited prognostic information and guide future medical management of the patient

The clinical methods of diagnostic testing for DFNB1 include (Smith and Van Camp, 2008):

- GJB2 (encoding Cx26) include:
  - Sequence analysis: This testing of the entire coding region detects both mutations of GJB2 in 98% of individuals with DFNB1.
  - Targeted mutation analysis: This testing will only look for a specific mutation and is generally not recommended.
- The clinical method of diagnostic testing for GJB6 (encoding Cx30) include targeted mutation analysis. This will detect the two large deletions that include a portion of GJB6, known to be the most common GJB6 mutation associated with DFNB1.

If only one GJB2 mutation is detected and a large deletion that includes a portion of GJB6 is not present, then it is thought that the affected individual is either: 1) deaf and coincidentally a carrier of GJB2 mutation; or 2) deaf with DFNB1 secondary to a novel non-GJB2 non-complementary mutation in the DFNB1 interval. There are other phenotypes associated with mutation in GJB2 and GJB6 (Smith and Van Camp, 2008).

The first step in testing of individuals with nonsyndromic hearing loss is sequence analysis of GJB2. If two deafness-causing mutations are identified, then the diagnosis of DFNB1 is established. If one mutation is identified, then targeted mutation analysis for the two deletions of GJB2 is warranted. If no deafness-causing mutation of GJB2 is identified, then targeted mutation analysis for GJB6 is not warranted. The frequency of these two deletions in all populations is not high enough to result in a large number of deaf persons homozygous for these mutations. They represent less than 0.5% of all individuals with prelingual deafness and without mutations in GJB2.

Chromosomal microarray analysis (CMA), a method of genetic testing, has been proposed to be used in genetic testing for nonsyndromic hearing loss. CMA is an emerging method of genetic testing that is also referred to as array comparative genomic hybridization, array CGH, or aCGH. It is a method that can identify small deletions and duplications of the subtelomeres, each pericentromeric region and other chromosome regions. There are few studies published in the literature that examine the use of this testing for this condition. They consist mainly of case studies or case series. The American College of Medical Genetics (ACMG) genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss note that microarray is an evolving technology and this method of testing is not included in their recommendations (ACMG 2002/2005). The use of this testing method in patients with congenital profound deafness is still preliminary and is not yet recommended.

### **Prenatal Testing and Preimplantation Genetic Diagnosis (PGD)**

The optimal time for determination of genetic risk, determination of carrier status and education regarding the availability of prenatal testing is before pregnancy. Requests for prenatal testing for conditions such as DFNB1 are not common. Prenatal diagnosis for pregnancies at risk is possible by analysis of the DNA extracted from fetal cells obtained by amniocentesis (performed at approximately 15–18 weeks' gestation) or chorionic villus sampling (CVS) (performed at approximately 10–12 weeks' gestation). It is important to note that both deafness-causing alleles of deaf family members must be identified before prenatal testing can be performed (Smith and Van Camp, 2008).

Preimplantation genetic diagnosis (PGD) refers to genetic testing of an early embryo resulting from in vitro fertilization. The testing is performed before implantation. PGD has recently been used as an alternative to prenatal testing with amniocentesis or chorionic villus sampling (CVS) techniques for detecting single gene disorders in embryos that have been identified as being at high risk for inheriting the gene disorder. PGD is available for families when a disease-causing mutation of gene GJB2 or GJB6 has been identified in one or both parents.

### **Professional Societies/Organizations**

The American College of Medical Genetics (ACMG) "Genetics Evaluation Guidelines for the Etiologic Diagnosis of Congenital Hearing Loss" (2002/2005) note that regarding syndromic deafness, the goal of triage/testing is to establish an etiologic basis for hearing loss in the most efficient manner possible. Recommendations included in the guidelines note that based on results of the genetic evaluation, the following should be considered (ACMG, 2002/2005):

- If a form of syndromic deafness is suspected: Gene-specific mutation screening can be obtained in many cases and more tests will undoubtedly become available.
- If nonsyndromic deafness is suspected and the patient is a simplex case:
  - CMV testing should be performed. A negative test for CMV antibodies in early infancy may exclude CMV-related hearing loss. A positive result must be interpreted with caution.
  - GJB2 (Cx26) mutation screening should be obtained by sequence analysis. A negative test result does not exclude a genetic etiology; a positive test result may make it possible to avoid other expensive and potentially invasive tests.
- If nonsyndromic deafness is suspected and the patient is a multiplex case with other hearing-impaired first-degree relatives, proceed directly to Cx26 testing.

### **Summary**

DFNB1 is characterized by congenital, nonprogressive, sensorineural hearing impairment. It is non-syndromic and autosomal recessive. Usually, the hearing impairment is severe or severe-to-profound, although families have been described in which affected persons have mild, moderate, or moderate-to-severe hearing loss. Diagnosis depends upon molecular genetic testing to identify deafness-causing mutations in the GJB2 gene and/or GJB6 that alter the gap junction beta-2 protein (connexin 26 [Cx26]) and the gap junction beta-6 protein (connexin 30 [Cx30]). GJB2 gene is the major gene responsible for nonsyndromic, recessive deafness. DFNB1 caused by mutations in GJB2 gene and GJB6 gene together account for 50% of autosomal recessive nonsyndromic hearing loss. Clinical uses of molecular genetic testing include diagnostic testing, carrier testing and prenatal diagnosis.

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## **Coding/Billing Information**

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

<b>CPT®*</b> <b>Codes</b>	<b>Description</b>
83890	Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA)
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid
83892	Molecular diagnostics; enzymatic digestion
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide)
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83909	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis)
83912	Molecular diagnostics; interpretation and report

<b>HCPCS</b> <b>Codes</b>	<b>Description</b>
S3844	DNA analysis of the connexin26 gene (GJB2) for susceptibility to congenital, profound deafness

<b>ICD-9-CM</b> <b>Diagnosis</b> <b>Codes</b>	<b>Description</b>
389.10	Unspecified sensorineural hearing loss
389.18	Sensorineural hearing loss, bilateral
389.7	Deaf, nonspeaking, not elsewhere classifiable
V19.2	Family history of other conditions; Deafness or hearing loss

**\*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

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## Policy History

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<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	12/15/2007	0254	Genetic Testing for Congenital, Profound Deafness

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