Cigna Medical Coverage Policy

Subject: Genetic Testing for Nonsyndromic Hearing Loss and Deafness (DFNB1)

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Table of Contents
- Coverage Policy: 1
- General Background: 2
- Coding/Billing Information: 5
- References: 6

Hyperlink to Related Coverage Policies
- Genetic Counseling
- Genetic Disease Screening Panels
- Genetic Testing of Heritable Disorders

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Coverage Policy

Cigna covers confirmatory (diagnostic) genetic testing as medically necessary for congenital, nonsyndromic, sensorineural, mild-to-profound deafness (DFNB1) when ALL of the following criteria are met:

- individual with congenital, nonprogressive, mild-to-profound bilateral hearing loss
- family history of hearing loss consistent with autosomal recessive or pseudodominant inheritance
- no findings of a syndromic hearing loss (i.e., not related to other medical problems)

with EITHER of the following tests:

- common deletion analysis of gene GJB6 (CPT code 81254), when sequence analysis of gene GJB2 has been performed, and only one mutation has been found

Cigna covers as medically necessary genetic testing for DFNB1 for a known familial mutation (i.e., testing for the known familial variant) for EITHER of the following indications:

- 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 blood relative with gene GJB2 or GJB6 mutation
  - when the individual is the reproductive partner of a known carrier of a disease-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 each parent is a known carrier of a GJB2 or GJB6 disease-causing mutation

Cigna does not cover genetic testing with multi-gene panels for nonsyndromic hearing loss because it is considered experimental, investigational or unproven.

*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.

All individuals undergoing genetic testing for DFNB1 should have both pre- and post-test genetic counseling with a board-certified or board-eligible medical geneticist or licensed or certified genetic counselor.

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, 2011):

- 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.

Molecular testing of gene GJB2 (which encodes the protein connexin 26) and GJB6 should be considered in the evaluation of individuals with congenital nonsyndromic sensorineural hearing loss consistent with autosomal recessive inheritance or in families with apparent "pseudodominant" inheritance of DFNB1. Pseudodominant inheritance refers to occurrence of an autosomal recessive disorder in two or more generations of a family; such inheritance tends to occur when the carrier rate in the general population is high. Molecular genetic testing of genes GJB2 and GJB6 should be performed in families with nonsyndromic hearing loss in which two generations are involved (Smith, et al., 2012).

In children with congenital severe-to-profound presumed autosomal recessive nonsyndromic hearing loss where mutations at the genes GJB2 and GJB6 at the DFNB1 locus are not identified, syndromic conditions, such as Usher syndrome type 1 should be considered if developmental motor milestones for sitting and walking independently are delayed (Smith, et al., 2012).

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, 2011). 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 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).

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, 2011).

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, 2011):
• 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 mutations in GJB2 and GJB6 (Smith and Van Camp, 2011).

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.

Multi-Gene Panel Testing for Non-Syndromic Hearing Loss
Multi-gene testing or screening with a panel of genetic tests has been proposed for to test for many causes of hearing loss. The testing is performed with several methods. Some tests utilize microarray technology to perform multi-gene testing, while others use variations of sequence analysis. The screening panels vary by laboratory in both in the techniques used and the number of genes sequenced. Some laboratories target only reported mutations in several genes, while other laboratories sequence all genes implicated in non-syndromic hearing loss (NSHL) (Smith, et al., 2012). Interpretation of the test results can be difficult, as there is a high likelihood of detecting one or more variants of unknown clinical significance (Brown, et al., 2012).

Available multi-gene screening panels include, but are not limited to:
• OtoSCOPE® is a test developed at the University of Iowa that tests for 66 genes that are known to cause non-syndromic hearing loss and syndromic conditions including Usher and Pendred syndrome.
• SoundGene™ Screening Panel (Pediatrix Medical Group Sunrise, FL) is a screening panel that identifies the most common causes of hearing loss.
• OtoGenome Test™ tests for 71 genes known to cause nonsyndromic hearing loss and syndromes that can present as nonsyndromic such as Usher, Pendred, Jervell and Lange-Nielsen (JLNS), and Branchio-Oto-Renal syndrome (BOR).

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 multi-gene panel 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. 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 (Rodriguez-Paris, et al., 2010; Gardener, et al., 2006; Shearer, et al., 2010). There is insufficient evidence in the published scientific literature to establish the diagnostic and clinical utility of multi-gene testing for non-syndromic hearing loss.

Genetic Counseling
Genetic testing should be undertaken only after independent genetic counseling has been provided to patients in order to assist in complex clinical decision-making. Post-genetic testing counseling should be planned. The genetic counseling should be provided by an independent specialty-trained genetics professional such as a medical geneticist or a genetic counselor who is an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counseling professional who is unaffiliated with the genetic testing lab performing the test(s).
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, 2011).

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.

Use Outside of the US
No relevant information found.

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 genes GJB2 and GJB6. 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.

The clinical utility of genetic testing with multi-gene screening panels has not been established. There is insufficient evidence in the published scientific literature to establish the diagnostic and clinical utility of multi-gene testing for nonsyndromic hearing loss.

Coding/Billing Information
Note: 1) This list of codes may not be all-inclusive.
   2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible
for reimbursement

**Covered when medically necessary:**

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<th>CPT® Codes</th>
<th>Description</th>
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<td>81252</td>
<td>GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence</td>
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<tr>
<td>81253</td>
<td>GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants</td>
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<tr>
<td>81254</td>
<td>GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])</td>
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| 81479      | Unlisted molecular pathology procedure  
  • GJB6 known familial variants |

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<th>HCPCS Codes</th>
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<td>S3844</td>
<td>DNA analysis of the connexin26 gene (GJB2) for susceptibility to congenital, profound deafness</td>
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**References**


24. Smith J, Shearer AE, Hildebrand MS, Van Camp G. Deafness and hereditary hearing loss overview. Gene Review. Funded by the NIH. Developed at the University of Washington, Seattle. Initial posting:
