



**GENETIC TESTING FOR  
NEUROFIBROMATOSIS (NF1)  
HS-135**



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**Genetic Testing for  
Neurofibromatosis (NF1)**

**Policy Number: HS-135**

**Original Effective Date: 10/1/2009**

**Revised Date(s): 10/29/2010; 9/15/2011**

**DISCLAIMER**

The Clinical Coverage Guideline is intended to supplement certain standard WellCare benefit plans. The terms of a member's particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member's benefit plan may contain specific exclusions related to the topic addressed in this Clinical Coverage Guideline. When a conflict exists between the two documents, the Member's Benefit Plan always supersedes the information contained in the Clinical Coverage Guideline. Additionally, Clinical Coverage Guidelines relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

**APPLICATION STATEMENT**

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

## **BACKGROUND**

*National Institutes of Health (NIH) Consensus Development Conference Criteria*

- 709.09** Six or more cafe-au-lait spots (CLSs) equal to or greater than 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in postpubertal patients;
- 237.71** Two or more neurofibromas of any type (or **215.9** - one plexiform neurofibroma);
- 709.09** Freckling in the axillary or inguinal regions;
- 192.0** One optic glioma (optic pathway glioma);
- 759.6** Two or more Lisch nodules (iris hamartomas);
- 733.90** Distinctive osseous lesion, such as sphenoid wing dysplasia or cortical thinning of the cortex of long bones, with or without pseudoarthrosis; **AND**
- V18.9** First-degree relative (parent, sibling, or child) with NF1

### *Genetic Background*

NF1 is inherited in an autosomal dominant fashion. In approximately one half of patients, the condition is caused by a new mutation in that conception. In such instances, neither parent has any clinical features of NF1, and the risk for recurrence of NF1 is likely not to exceed 1%. Rare instances of recurrence from phenotypically unaffected parents are attributed to germ-line or somatic mosaicism. However, individuals with NF1 caused by a new mutation are at a 50% risk of transmitting the gene to each of their offspring. The NF1 gene has a high penetrance rate; therefore, an individual who carries the mutation can be expected to have clinical manifestations of the disorder. Some individuals are mosaic for an NF1 mutation and may have localized signs, referred to as "segmental neurofibromatosis." These individuals may be at risk of transmitting the mutant gene to their offspring if the germ line includes cells with the mutation, which results in an increased risk of NF1 in their offspring.

The NF1 gene is located on the long arm of chromosome 17 at band q11.2. Neurofibromin, the protein product of the normal gene, acts as a tumor suppressor by down-regulating another cell protein, Ras that enhances cell growth and proliferation. A wide variety of mutations have been identified within the NF1 gene, which give rise to diminished function of neurofibromin in affected persons. Detection of mutations in the NF1 gene by DNA analysis has proven to be complex because of the gene's large size, presence of pseudogenes, and great variety of possible abnormalities.

### *Complications Associated with NF1*

Although most individuals with NF1 are mildly affected, a risk of significant morbidity and life-threatening problems exists and cannot be predicted on the basis of findings in childhood. Serious complications of NF1 can result from direct involvement of multiple organ systems by plexiform neurofibromas. In addition, the lifelong risk of malignancy in affected individuals is increased. Malignant peripheral nerve sheath tumors represent the most common neoplasm, occurring in approximately 5% to 10% of individuals with NF1. They usually develop in adulthood and are heralded by the presence of pain or rapid growth of a plexiform or deep nodular neurofibroma; however, similar manifestations can occur with a benign lesion. Other malignancies occur less frequently in patients with NF1, including pheochromocytoma, rhabdomyosarcoma, leukemia, and brain tumors other than optic glioma.

Other associations exist with NF1, such as vascular changes. Macrocephaly affects most individuals with NF1. Short stature occurs in one third of individuals with NF1 and does not seem to be related to disease severity. Height-growth velocity is normal for both genders during childhood, but the pubertal growth spurt is slightly reduced. Growth charts made specifically for children with NF1 are available. Neurofibromas develop in the gastrointestinal tract in a small proportion of patients with NF1 and usually present after early childhood. They may cause bleeding and anemia or signs of functional or mechanical obstruction. Rare forms of intra-abdominal secretory or nonsecretory neoplasms also represent low-frequency associations. Evaluation for gastrointestinal complications should be pursued in the presence of unexplained anemia or weight loss, abdominal bloating, sudden or persistent abdominal

pain, chronic diarrhea, signs of malabsorption, gastrointestinal bleeding, or recurrent emesis. Seizures occur in 6% to 7% of cases. Although electroencephalographic abnormalities are commonly reported, electroencephalography is not routinely recommended. If seizures are present, an intracranial tumor must be excluded, although usually no etiology is found. Nonossifying fibromas of the long bones and especially the distal femur and proximal tibia, on occasion, occur in adolescence or adulthood and can result in fracture. Therefore, a screening radiograph of both knees may be considered in early adolescence to provide appropriate intervention for individuals in whom lesions are detected. Scoliosis is present in 10% to 30% of NF1 cases. Both idiopathic and dystrophic forms occur and can lead to diminished pulmonary function. Variability in progression, however, makes it difficult to determine the prognosis once scoliosis is detected, and close monitoring is necessary after it has been discovered. An increased risk for osteoporosis in adulthood also exists. Hypertension affects approximately 4% of individuals with NF1. Although essential hypertension is the most common cause of hypertension, in NF1 it can also result from renovascular disease, tumors that secrete vasoactive compounds, and coarctation of the aorta. Therefore, monitoring blood pressure on a yearly basis is indicated, and if hypertension is found, additional evaluation and treatment or referral to an appropriate specialist for management is indicated.

NF1 is associated with an increased incidence of mental retardation (4%–8%); however, in most instances, intellectual abilities are in the average to low-average range. In contrast, specific learning disabilities are observed in as many as 40% to 60% of affected children, and impaired performance on at least 1 test of academic achievement is present in 65% of children with NF1. Deficits in visual-spatial-perceptual skills can result in reading and spelling difficulties. Poor fine-motor coordination can lead to problems with handwriting. Attention-deficit/hyperactivity disorder also occurs more frequently in children with NF1. Children with NF1 have a higher likelihood of being hypotonic and of having subtle neurologic abnormalities that affect balance and gait. Speech problems also may occur, and an association with velopharyngeal insufficiency exists.

For the NF1 genetic test, Hayes (2010) gives a rating of D for confirmation of the NF1 diagnosis in patients fulfilling the clinical diagnostic criteria and for establishing a diagnosis of NF1 in symptomatic patients who do not fulfill the clinical diagnostic criteria. A rating of C was given for the prenatal or preimplantation genetic diagnosis of NF1 in the pregnancies of affected individuals. The same rating was also given for identification of the causative gene variant in NF1 patients desiring prenatal or preimplantation genetic diagnosis (or the testing of other at-risk family members).

## **POSITION STATEMENT**

Genetic testing for the diagnosis of neurofibromatosis 1 (NF1) **is considered medically necessary if the following criteria are met:**

- Initial diagnosis using the National Institutes of Health (NIH) Consensus Development Conference criteria (see below) is inconclusive\*; **AND,**
- Results of the test will directly affect the treatment of the affected member; **AND,**
- The member will receive genetic counseling before testing occurs

NOTE: Molecular testing is typically not indicated because a diagnosis of NF1 in 95% of cases can be established on the basis of clinical findings alone by 11 years of age.

Genetic and molecular testing for NF1 **is considered NOT medically necessary for all other circumstances, including prenatal testing.**

## **CODING**

### **CPT® Codes**

- 83891** Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (DNA or RNA)  
**83894** Molecular diagnostics; separation by gel electrophoresis, each nucleic acid type (agarose or polyacrylamide)  
**83896** Molecular diagnostics; nucleic acid probe, each  
**83898** Molecular diagnostics; amplification, target, each nucleic acid sequence  
**83900** Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences  
**83902** Molecular diagnostics; reverse transcription  
**83903** Molecular diagnostics; mutation scanning by physical properties (single strand conformational polymorphisms [SSCP], heteroduplex, denaturing gradient gel electrophoresis [DGGE], RNA'aseA), single segment, each  
**83904** Molecular diagnostics; mutation identification by sequencing, single segment, each segment  
**83909** Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis) each nucleic acid preparation  
**83912** Molecular diagnostics; interpretation and report  
**83913** Molecular diagnostics; RNA stabilization  
**88230** Tissue Culture for non-neoplastic disorders; lymphocyte

**ICD-9-CM Procedure Codes** - No applicable codes

**HCPCS Level II ©Codes** - No applicable codes

### **ICD-9-CM Diagnosis Codes**

- V18.9** Family history of genetic disease carrier  
**V26.33** Genetic counseling

\*Current Procedural Terminology (CPT) © 2011 American Medical Medical Association: Chicago, IL.

## **REFERENCES**

### **Peer Reviewed**

1. Hersh, J.H. & American Academy of Pediatrics Committee on Genetics. (2008). Health supervision for children with neurofibromatosis. *Pediatrics*, 121(3), 633-642.
2. Hayes Directory. (2010, November 17). GTE Report: neurofibromatosis type 1 (NF1). Retrieved from <http://www.hayesinc.com>
3. McKeever, K., Shepherd, C.W., Crawford, H., & Morrison, P.J. (2008). An epidemiological, clinical and genetic survey of Neurofibromatosis type 1 in children under sixteen years of age. *Ulster Medical Journal*, 77(3), 160-163.

### **Government Agencies, Professional and Medical Organizations**

1. N.A. (1987, July). National Institutes of Health Consensus development conference statement: neurofibromatosis. *Neurofibromatosis*, 1(3), 172-178.

## **HISTORY AND REVISIONS**

<b>Date</b>	<b>Action</b>
12/1/2011	• New template design approved by MPC.
9/15/2011	• Approved by MPC. • Added Hayes rating from 2010 and one new reference.