FEP Medical Policy Manual

FEP 2.04.137 Genetic Testing for Neurofibromatosis

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Related Policies:

None

Genetic Testing for Neurofibromatosis

Description

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Neurofibromatoses are autosomal dominant genetic disorders associated with tumors of the peripheral and central nervous systems. There are 3 clinically and genetically distinct forms: neurofibromatosis (NF) type 1, NF type 2-related schwannomatosis (formerly NF type 2), and schwannomatosis. The potential benefit of genetic testing for NF type 1 (*NF1*), neurofibromatosis type 2 (*NF2*), or *SPRED1* pathogenic variants is to confirm the diagnosis in an individual with suspected NF who does not fulfill clinical diagnostic criteria or to determine future risk of NF in asymptomatic at-risk relatives.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for neurofibromatosis type 1 (*NF1*), neurofibromatosis type 2-related schwannomatosis (formerly NF type 2)(*NF2*), or *SPRED1* pathogenic variants improves the net health outcome in individuals who are suspected of having or who are at risk of developing neurofibromatosis.

POLICY STATEMENT

Genetic testing for neurofibromatosis type 1 (*NF1*) or neurofibromatosis type 2-related schwannomatosis (formerly NF type 2)(*NF2*) pathogenic variants may be considered **medically necessary** when a diagnosis of neurofibromatosis is clinically suspected due to signs of disease, but a definitive diagnosis cannot be made without genetic testing.

Genetic testing for *NF1* or *NF2* pathogenic variants in at-risk relatives, with no signs of disease, may be considered **medically necessary** when a definitive diagnosis cannot be made without genetic testing AND at least one of the following criteria is met:

- A close relative (ie, first-, second-, or third-degree relative) has a known *NF1* or *NF2* variant; or
- A close relative has been diagnosed with neurofibromatosis but whose genetic status is unavailable.

Genetic testing for neurofibromatosis for all other situations not meeting the criteria outlined above is considered **investigational**.

POLICY GUIDELINES

Testing Strategy

For evaluation of neurofibromatosis type 1 (*NF1*), testing for a variety of pathogenic variants of *NF1,* preferably through a multistep variant detection protocol, is indicated. If no *NF1* pathogenic variants are detected in patients with suspected NF1, testing for *SPRED1* variants is reasonable.

There are a number of cancer types associated with NF, including breast cancer associating with *NF1*. While the National Comprehensive Cancer Network's Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic consensus guidelines (version 2.2024) addresses the risk of breast cancer with *NF1* and has intensified breast cancer screening recommendations, these screening recommendations apply only to individuals with a clinical diagnosis of NF1.[1,] Criteria for a clinical diagnosis are included below.

Definitions

Mutation Scanning

Mutation scanning is a process by which a particular segment of DNA is screened to identify sequence variants. Variant gene regions are then further analyzed (eg, by sequencing) to identify the sequence alteration. Mutation scanning allows for screening of large genes and novel sequence variants.

Schwann Cells

Schwann cells cover the nerve fibers in the peripheral nervous system and form the myelin sheath.

Simplex Disease

Simplex disease is a single occurrence of a disease in a family.

Somatic Mosaicism

Somatic mosaicism is the occurrence of 2 genetically distinct populations of cells within an individual, derived from a postzygotic variant. Unlike inherited variants, somatic mosaic variants may affect only a portion of the body and are not transmitted to progeny.

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual"s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient"s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

When possible, genetic testing for neurofibromatosis should be performed in an affected family member so that testing in at-risk family members with no signs of disease can be performed for the family-specific variant found in the affected family member. However, coverage for testing of the affected index case (proband) depends on contract benefit language.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Lab tests for NF are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals who have suspected neurofibromatosis (NF) who receive genetic testing for *NF1*, *NF2,* or *SPRED1* pathogenic variants, the evidence includes clinical validation studies of a multistep diagnostic protocol and genotype-phenotype correlation studies. Relevant outcomes are test accuracy and validity, symptoms, morbid events, and functional outcomes. A multistep variant testing protocol identifies more than 95% of pathogenic variants in NF type 1; for NF type 2, the variant detection rate approaches more than 70% in simplex cases and exceeds 90% for familial cases. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic, with a close relative(s) with an NF diagnosis, who receive genetic testing for *NF1*, *NF2,* or *SPRED1* pathogenic variants, there is no direct evidence. Relevant outcomes are test accuracy and validity, symptoms, morbid events, and functional outcomes. For individuals with a known pathogenic variant in the family, testing of at-risk relatives will confirm or exclude the variant with high certainty. While direct evidence on the clinical utility of genetic testing for NF is lacking, a definitive diagnosis resulting from genetic testing can direct patient care according to established clinical management guidelines, including referrals to the proper specialists, treatment of manifestations, and surveillance. Testing of at-risk relatives will lead to initiation or avoidance of management and/or surveillance. Early surveillance may be particularly important for patients with NF type 2 because early identification of internal lesions by imaging is expected to improve outcomes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Pediatrics

In 2019, the American Academy of Pediatrics published diagnostic and health supervision guidance for children with neurofibromatosis type 1 (NF1).[40,] The guidance makes the following statements related to genetic testing:

"NF1 genetic testing may be performed for purposes of diagnosis or to assist in genetic counseling and family planning. If a child fulfills diagnostic criteria for NF1, molecular genetic confirmation is usually unnecessary. For a young child who presents only with [caf-au-lait macules], NF1 genetic testing can confirm a suspected diagnosis before a second feature, such as skinfold freckling, appears. Some families may wish to establish a definitive diagnosis as soon as possible and not wait for this second feature, and genetic testing can usually resolve the issue" and "Knowledge of the NF1 [pathogenic sequence variant] can enable testing of other family members and prenatal diagnostic testing."

The guidance includes the following summary and recommendations about genetic testing:

- can confirm a suspected diagnosis before a clinical diagnosis is possible;
- can differentiate NF1 from Legius syndrome;
- may be helpful in children who present with atypical features;
- usually does not predict future complications; and
- may not detect all cases of NF1; a negative genetic test rules out a diagnosis of NF1 with 95% (but not 100%) sensitivity

National Comprehensive Cancer Network

The National Comprehensive Cancer Network's Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic consensus guidelines (version 2.2024) address the association between pathogenic *NF1* variants and risk of breast cancer.[1,] The panel recommends annual screening mammograms for breast cancer beginning at age 30 years (or younger, if indicated according to family history of breast cancer) in patients with such *NF1* variants, with consideration for screening via breast magnetic resonance imaging (MRI) through age 50 due to excess risk between the ages of 30 and 50, and referral to an NF1 specialist for evaluation and management of other *NF1*-associated cancer risks. The guidelines state that studies show that beginning at age 50 breast cancer risk in women with NF1 may not significantly differ from that of women in the general population; and, therefore, breast MRI screening in patients with NF1 may be discontinued at 50 years of age. Note that these screening recommendations apply only to individuals with a clinical diagnosis of NF1.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 2.2024. Accessed November 20, 2023.
2. Friedman JM. Neurofibromatosis 1. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. GeneReviews. Seattle, WA: University of Washington; 1993-2023. Updated April 21, 2022. Accessed November 21, 2023.
3. Uusitalo E, Rantanen M, Kallionp RA, et al. Distinctive Cancer Associations in Patients With Neurofibromatosis Type 1. J Clin Oncol. Jun 10 2016; 34(17): 1978-86. PMID 26926675
4. Walker L, Thompson D, Easton D, et al. A prospective study of neurofibromatosis type 1 cancer incidence in the UK. Br J Cancer. Jul 17 2006; 95(2): 233-8. PMID 16786042
5. Nishida T, Tsujimoto M, Takahashi T, et al. Gastrointestinal stromal tumors in Japanese patients with neurofibromatosis type I. J Gastroenterol. Jun 2016; 51(6): 571-8. PMID 26511941
6. Stiller CA, Chessells JM, Fitchett M. Neurofibromatosis and childhood leukaemia/lymphoma: a population-based UKCCSG study. Br J Cancer. Nov 1994; 70(5): 969-72. PMID 7947106
7. Niemeyer CM, Arico M, Basso G, et al. Chronic myelomonocytic leukemia in childhood: a retrospective analysis of 110 cases. European Working Group on Myelodysplastic Syndromes in Childhood (EWOG-MDS). Blood. May 15 1997; 89(10): 3534-43. PMID 9160658
8. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol. May 1988; 45(5): 575-8. PMID 3128965
9. Legius E, Messiaen L, Wolkenstein P, et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med. Aug 2021; 23(8): 1506-1513. PMID 34012067
10. Bernier A, Larbrisseau A, Perreault S. Caf-au-lait Macules and Neurofibromatosis Type 1: A Review of the Literature. Pediatr Neurol. Jul 2016; 60: 24-29.e1. PMID 27212418
11. Hersh JH. Health supervision for children with neurofibromatosis. Pediatrics. Mar 2008; 121(3): 633-42. PMID 18310216
12. Legius E, Stevenson D. Legius Syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. GeneReviews. Seattle, WA: University of Washington; 1993-2023. Updated August 6, 2020. Accessed November 21, 2023.
13. Evans DG. NF2-Related Schwannomatosis. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. GeneReviews. Seattle, WA: University of Washington; 1993-2023. Updated April 20, 2023. Accessed November 20, 2023.
14. Evans DG, Sainio M, Baser ME. Neurofibromatosis type 2. J Med Genet. Dec 2000; 37(12): 897-904. PMID 11106352
15. Plotkin SR, Messiaen L, Legius E, et al. Updated diagnostic criteria and nomenclature for neurofibromatosis type 2 and schwannomatosis: An international consensus recommendation. Genet Med. Sep 2022; 24(9): 1967-1977. PMID 35674741
16. Dhamija R, Plotkin S, Gomez A, Babovic-Vuksanovic D. LTRZ1- and SMARCB1-Related Schwannomatosis. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews. Seattle, WA: University of Washington; 1993-2023. Updated July 27, 2023. Accessed November 20, 2023.
17. van Minkelen R, van Bever Y, Kromosoeto JN, et al. A clinical and genetic overview of 18 years neurofibromatosis type 1 molecular diagnostics in the Netherlands. Clin Genet. Apr 2014; 85(4): 318-27. PMID 23656349
18. Sabbagh A, Pasmant E, Imbard A, et al. NF1 molecular characterization and neurofibromatosis type I genotype-phenotype correlation: the French experience. Hum Mutat. Nov 2013; 34(11): 1510-8. PMID 23913538
19. Valero MC, Martn Y, Hernndez-Imaz E, et al. A highly sensitive genetic protocol to detect NF1 mutations. J Mol Diagn. Mar 2011; 13(2): 113-22. PMID 21354044
20. Spurlock G, Bennett E, Chuzhanova N, et al. SPRED1 mutations (Legius syndrome): another clinically useful genotype for dissecting the neurofibromatosis type 1 phenotype. J Med Genet. Jul 2009; 46(7): 431-7. PMID 19443465
21. Zhu L, Zhang Y, Tong H, et al. Clinical and Molecular Characterization of NF1 Patients: Single-Center Experience of 32 Patients From China. Medicine (Baltimore). Mar 2016; 95(10): e3043. PMID 26962827
22. Zhang J, Tong H, Fu X, et al. Molecular Characterization of NF1 and Neurofibromatosis Type 1 Genotype-Phenotype Correlations in a Chinese Population. Sci Rep. Jun 09 2015; 5: 11291. PMID 26056819
23. Bianchessi D, Morosini S, Saletti V, et al. 126 novel mutations in Italian patients with neurofibromatosis type 1. Mol Genet Genomic Med. Nov 2015; 3(6): 513-25. PMID 26740943
24. Cal F, Chiavetta V, Ruggeri G, et al. Mutation spectrum of NF1 gene in Italian patients with neurofibromatosis type 1 using Ion Torrent PGM™ platform. Eur J Med Genet. Feb 2017; 60(2): 93-99. PMID 27838393
25. Giugliano T, Santoro C, Torella A, et al. Clinical and Genetic Findings in Children with Neurofibromatosis Type 1, Legius Syndrome, and Other Related Neurocutaneous Disorders. Genes (Basel). Jul 31 2019; 10(8). PMID 31370276
26. Angelova-Toshkina D, Holzapfel J, Huber S, et al. Neurofibromatosis type 1: A comparison of the 1997 NIH and the 2021 revised diagnostic criteria in 75 children and adolescents. Genet Med. Sep 2022; 24(9): 1978-1985. PMID 35713653
27. Pasmant E, Sabbagh A, Spurlock G, et al. NF1 microdeletions in neurofibromatosis type 1: from genotype to phenotype. Hum Mutat. Jun 2010; 31(6): E1506-18. PMID 20513137
28. Mautner VF, Kluwe L, Friedrich RE, et al. Clinical characterisation of 29 neurofibromatosis type-1 patients with molecularly ascertained 1.4 Mb type-1 NF1 deletions. J Med Genet. Sep 2010; 47(9): 623-30. PMID 20543202
29. Upadhyaya M, Huson SM, Davies M, et al. An absence of cutaneous neurofibromas associated with a 3-bp inframe deletion in exon 17 of the NF1 gene (c.2970-2972 delAAT): evidence of a clinically significant NF1 genotype-phenotype correlation. Am J Hum Genet. Jan 2007; 80(1): 140-51. PMID 17160901
30. Rojnueangnit K, Xie J, Gomes A, et al. High Incidence of Noonan Syndrome Features Including Short Stature and Pulmonic Stenosis in Patients carrying NF1 Missense Mutations Affecting p.Arg1809: Genotype-Phenotype Correlation. Hum Mutat. Nov 2015; 36(11): 1052-63.

PMID 26178382
31. Pinna V, Lanari V, Daniele P, et al. p.Arg1809Cys substitution in neurofibromin is associated with a distinctive NF1 phenotype without neurofibromas. Eur J Hum Genet. Aug 2015; 23(8): 1068-71. PMID 25370043
32. Hutter S, Piro RM, Waszak SM, et al. No correlation between NF1 mutation position and risk of optic pathway glioma in 77 unrelated NF1 patients. Hum Genet. May 2016; 135(5): 469-475. PMID 26969325
33. Ko JM, Sohn YB, Jeong SY, et al. Mutation spectrum of NF1 and clinical characteristics in 78 Korean patients with neurofibromatosis type 1. Pediatr Neurol. Jun 2013; 48(6): 447-53. PMID 23668869
34. Pasmant E, Sabbagh A, Hanna N, et al. SPRED1 germline mutations caused a neurofibromatosis type 1 overlapping phenotype. J Med Genet. Jul 2009; 46(7): 425-30. PMID 19366998
35. Messiaen L, Yao S, Brems H, et al. Clinical and mutational spectrum of neurofibromatosis type 1-like syndrome. JAMA. Nov 18 2009; 302(19): 2111-8. PMID 19920235
36. Wallace AJ, Watson CJ, Oward E, et al. Mutation scanning of the NF2 gene: an improved service based on meta-PCR/sequencing, dosage analysis, and loss of heterozygosity analysis. Genet Test. 2004; 8(4): 368-80. PMID 15684865
37. Evans DG, Ramsden RT, Shenton A, et al. Mosaicism in neurofibromatosis type 2: an update of risk based on uni/bilaterality of vestibular schwannoma at presentation and sensitive mutation analysis including multiple ligation-dependent probe amplification. J Med Genet. Jul 2007; 44(7): 424-8. PMID 17307835
38. Evans DG. NF2-related schwannomatosis (formerly neurofibromatosis type 2). In: UpToDate, ed. UpToDate. Waltham, MA: Kluwer Wolters; Updated November 2, 2023. Accessed November 20, 2023.
39. Selvanathan SK, Shenton A, Ferner R, et al. Further genotype--phenotype correlations in neurofibromatosis 2. Clin Genet. Feb 2010; 77(2): 163-70. PMID 19968670
40. Miller DT, Freedenberg D, Schorry E, et al. Health Supervision for Children With Neurofibromatosis Type 1. Pediatrics. May 2019; 143(5). PMID 31010905

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2018	New policy	Genetic testing for neurofibromatosis (NF) may be considered medically necessary in individuals with suspected NF.
March 2019	Replace policy	Policy updated with literature review through October 30, 2018; no references added. Policy statements unchanged.
March 2020	Replace policy	Policy updated with literature review through November 20, 2019; references added. Policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through November 20, 2020; no references added. Policy statement edited to clarify that genetic testing refers to testing for pathogenic variants in NF1 and NF2 genes; statements otherwise unchanged.
March 2022	Replace policy	Policy updated with literature review through December 17, 2021; no references added. Policy statements unchanged.
March 2023	Replace policy	Policy updated with literature review through November 21, 2022; references added. Minor editorial refinement to policy statements; intent unchanged.
March 2024	Replace policy	Policy updated with literature review through November 20, 2023; no references added. Minor editorial refinement to policy statements; intent unchanged.