FEP Medical Policy Manual

FEP 2.04.137 Genetic Testing for Neurofibromatosis

Effective Policy Date: April 1, 2021

Original Policy Date: April 2018

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, 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 *NF1*, *NF2,* or *SPRED1* pathogenic variants improves the net health outcome in individuals who are suspected of having NF.

POLICY STATEMENT

Genetic testing for neurofibromatosis type 1 (*NF1*) or neurofibromatosis 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.

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.

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 patients 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

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 a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

In 2019, the American Academy of Pediatrics published diagnostic and health supervision guidance for children with neurofibromatosis type 1 (NF1).[28.] 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

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.

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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.