CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH

DIAGNOSTIC CRITERIA FOR SCHWANNOMATOSIS

2022 UPDATE FOR NEUROFIBROMATOSIS TYPE 2 (NF2) AND SCHWANNOMATOSIS

The Children's Tumor Foundation (CTF) along with an international group of NF experts, reviewed and updated the diagnostic criteria of neurofibromatosis type 2 (NF2) and schwannomatosis (SWN) to include the latest in NF research and clinical findings. The goal of these efforts was to improve diagnostic accuracy and therefore provide appropriate medical care. The new criteria are not just for NF specialists but all general practitioners.

WHY REVISE THE DIAGNOSTIC CRITERIA?

The criteria for NF2 was first established by the National Institutes of Health in 1988, as well as a UK revision of NF2 in 1992, and the first-published SWN criteria in 2005. Reasons for updating the criteria in 2022 include:

- Challenges in distinguishing the types of neurofibromatosis and schwannomatosis
- Discovery of the genes involved in NF2 and SWN
- Increased access to genetic testing
- Recent studies discovered significant overlap in the features of NF2 and SWN
- New awareness of tumor types associated with and not associated with NF2 and SWN

UPDATING THE TERMS: NF2 AND SCHWANNOMATOSIS

The former diagnostic criteria for NF2 and schwannomatosis classified patients primarily based on clinical features; however, it is now apparent that the manifestations of these diseases span the same continuum. For this reason, "schwannomatosis" no longer defines a distinct syndrome, but is now used as an umbrella term to describe the overlapping conditions in which a patient has many schwannomas. Retiring "NF2" will also minimize misdiagnosis with neurofibromatosis type 1.

The updated diagnostic criteria for schwannomatosis classify each disorder according to the specific gene harboring a pathogenic variant (formerly called a gene mutation). Therefore, the standard nomenclature will be of the form: *GENE*-related schwannomatosis (gene names are in italics). This format will allow us to add additional types of schwannomatosis as new genes are identified.

- ***NF2*-related schwannomatosis** (formerly called NF2)
- ***SMARCB1*-related schwannomatosis**
- ***LZTR1*-related schwannomatosis**
- **22q-related schwannomatosis**
- **Schwannomatosis NOS** (not otherwise specified) for patients who have not had genetic testing
- **Schwannomatosis NEC** (not elsewhere classified) for patients in whom genetic testing of blood/saliva and tumors failed to detect a pathogenic variant

GENETIC ANALYSIS FOR SCHWANNOMATOSIS

Molecular testing for the genes known to be involved in all types of schwannomatosis is available, and should be completed whenever possible for a patient suspected of SWN. Testing is required for the diagnosis of a specific type of schwannomatosis, except *NF2*-related schwannomatosis, which does not require genetic testing if clinical criteria are met. Genetic analysis can be performed on a blood or saliva sample, but often requires tumor tissue if available. The penetrance of *LZTR1*- and *SMARCB1*-related schwannomatosis is reduced, and pathogenic variants in these genes may be associated with other phenotypes. Consultation with a healthcare provider with genetics expertise may therefore be beneficial in some cases.

More information about the revised criteria can be found at **ctf.org/criteria**.

2022 UPDATES

DIAGNOSTIC CRITERIA FOR *NF2*-RELATED SCHWANNOMATOSIS

Formerly called Neurofibromatosis Type 2 (NF2)

A diagnosis of *NF2*-related schwannomatosis can be made when a patient has **one of the following**:

- Bilateral vestibular schwannomas (VS)
- An identical *NF2* pathogenic variant* in at least two anatomically distinct *NF2*-related tumors (schwannoma, meningioma, and/or ependymoma)
- Either **two Major** OR **one Major and two Minor** criteria are present as follows:

MAJOR CRITERIA

- Unilateral vestibular schwannoma
- First-degree relative other than a sibling with *NF2*-related schwannomatosis
- Two or more meningiomas. (Note: single meningioma qualifies as a minor criterion)
- *NF2* pathogenic variant* in an unaffected tissue such as blood

**When the variant is present at significantly less than 50%, the diagnosis is mosaic NF2-related schwannomatosis*

MINOR CRITERIA

Can count more than one of a type (e.g., two schwannomas = two minor criteria)

- Ependymoma; schwannoma (Note: if the major criterion is unilateral VS, at least one schwannoma must be dermal in location)

Can count only once

- Juvenile subcapsular or cortical cataract; retinal hamartoma; epiretinal membrane in a person aged less than 40 years; meningioma (Note: multiple meningiomas qualify as a major criterion; meningioma cannot be used as both a major and a minor criteria)

KEY UPDATES TO FORMER NF2 DIAGNOSTIC CRITERIA:

- Added *NF2* pathogenic variant
- Clarified first degree relative with "other than sibling"
- Cataract clarified to juvenile cataract
- Added retinal hamartoma as criterion
- Removed glioma and neurofibroma, and added ependymoma

2022 UPDATES

ADDITIONAL GENETIC CRITERIA UPDATES:

- Genetic analysis in blood or saliva may identify pathogenic *NF2* variants in 66%–90% of individuals
- Genetic analysis is NOT required for diagnosis for *NF2*-related schwannomatosis if clinical criteria are met
- Genetic analysis with family history is sufficient to diagnose *NF2*-related schwannomatosis (no requirement to have clinical manifestations)

DIAGNOSTIC CRITERIA FOR MOSAIC SCHWANNOMATOSIS:

Mosaicism is confirmed for *LZTR1*-related, *SMARCB1*-related, or *NF2*-related schwannomatosis by **either** of the following:

- Clearly less than 50% pathogenic variant allele fraction (VAF) in blood or saliva

OR

- Pathogenic variant not detected in blood or saliva but shared pathogenic variant in two or more anatomically unrelated tumors

DIAGNOSTIC CRITERIA FOR *SMARCB1*-RELATED SCHWANNOMATOSIS

Previously classified as "schwannomatosis with *SMARCB1* mutation"

A diagnosis of ***SMARCB1*-related schwannomatosis** can be made when a patient meets **one of the following criteria**:

- At least one pathologically confirmed schwannoma or hybrid nerve sheath tumor AND a *SMARCB1* pathogenic variant in an unaffected tissue such as blood or saliva
- A common *SMARCB1* pathogenic variant in two anatomically distinct schwannomas or hybrid nerve sheath tumors

Note: diagnosis requires surgical specimen to confirm tumor histology

DIAGNOSTIC CRITERIA FOR *LZTR1*-RELATED SCHWANNOMATOSIS

Previously classified as "schwannomatosis with *LZTR1* mutation"

A diagnosis of ***LZTR1*-related schwannomatosis** can be made when a patient meets **one of the following criteria**:

- At least one pathologically confirmed schwannoma or hybrid nerve sheath tumor AND an *LZTR1* pathogenic variant in an unaffected tissue such as blood or saliva
- A common *LZTR1* pathogenic variant in two anatomically distinct schwannomas or hybrid nerve sheath tumors

Note: diagnosis requires surgical specimen to confirm tumor histology

2022 UPDATES

DIAGNOSTIC CRITERIA FOR 22q-RELATED SCHWANNOMATOSIS

Previously classified as "schwannomatosis without identified mutation in blood"

A diagnosis of **22q-related schwannomatosis** can be made when an individual does not meet criteria for *NF2*-related schwannomatosis, *SMARCB1*-related schwannomatosis, or *LTZR1*-related schwannomatosis, **and has both of the following molecular features**:

- Loss of heterozygosity (LOH) of the same chromosome 22q markers in two anatomically distinct schwannomas or hybrid nerve sheath tumors AND
- A different *NF2* pathogenic variant in each tumor which cannot be detected in unaffected tissue

Note: diagnosis requires at least two surgical specimens

DIAGNOSTIC CRITERIA FOR SCHWANNOMATOSIS NOS AND SCHWANNOMATOSIS NEC

A diagnosis of **schwannomatosis-NOS** (not otherwise specified) can be made if **both of the following** criteria are met and genetic testing was not performed or is not available:

- presence of two or more lesions on appropriate imaging consistent with non-intradermal schwannomas, and
- pathologic confirmation of at least one schwannoma or hybrid nerve sheath tumor

A diagnosis of **schwannomatosis-NEC** (not elsewhere classified) can be made if **both of the above** criteria are met and genetic testing does not reveal a pathogenic variant in known schwannomatosis-related genes.

CHILDREN'S TUMOR FOUNDATION
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More information including a link to the publication about the 2022 updates to the diagnostic criteria for all types of neurofibromatosis and schwannomatosis can be found at ctf.org/criteria.

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DIAGNOSTIC CRITERIA FOR *NF2*-RELATED SCHWANNOMATOSIS

2022 UPDATE

CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH

NF2-RELATED SCHWANNOMATOSIS

A diagnosis of NF2-related schwannomatosis can be made when a patient has **one of the following**:

» **Bilateral vestibular schwannomas (VS)**

» An identical ***NF2* pathogenic variant*** in at least two anatomically distinct *NF2*-related tumors (schwannoma, meningioma, and/or ependymoma)

» When either **two Major OR one Major** and **two Minor** criteria are present as follows:

MAJOR CRITERIA

» Unilateral vestibular schwannoma (VS)

» First-degree relative other than a sibling with *NF2*-related schwannomatosis

» Two or more meningiomas (Note: single meningioma qualifies as a minor criterion)

» *NF2* pathogenic variant* in an unaffected tissue such as blood or saliva

** When the variant is present at significantly less than 50%, the diagnosis is mosaic NF2-related schwannomatosis*

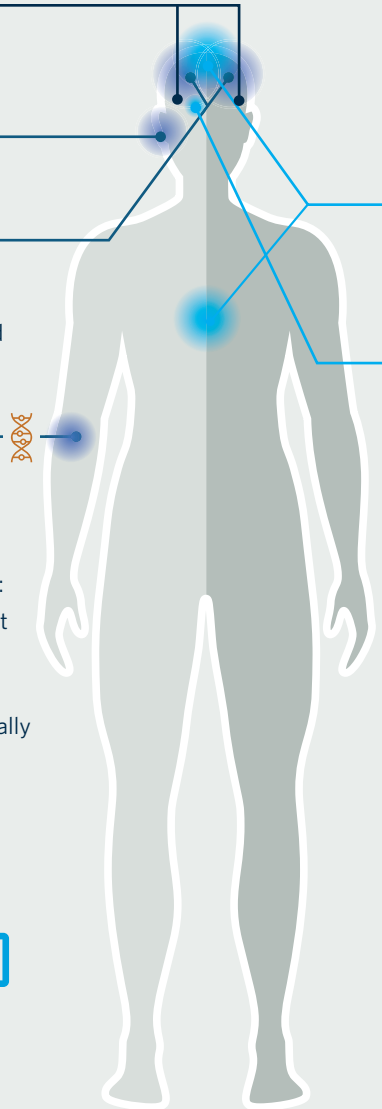
Mosaicism

Mosaicism is confirmed for NF2-related schwannomatosis by **either** of the following:

» Clearly less than 50% pathogenic variant allele fraction in blood or saliva

OR

» Pathogenic variant not detected in clinically unaffected tissue but shared pathogenic variant in two or more anatomically unrelated tumors



MINOR CRITERIA

Can count more than once of each type (e.g., two schwannomas = two minor criteria)

» Ependymoma; schwannoma (Note: if the major criterion is unilateral vestibular schwannomas, at least one schwannoma must be dermal in location)

Can count only once

» Juvenile subcapsular or cortical cataract; retinal hamartoma; epiretinal membrane in a person aged less than 40 years; meningioma (Note: multiple meningiomas qualify as a major criteria; meningioma cannot be used as both a major and minor criterion)

ADDITIONAL GENETIC CRITERIA:

» Genetic analysis may identify pathogenic *NF2* variants in blood in 66%-90% of individuals

» Genetic analysis is not REQUIRED for diagnosis. It will be possible to diagnose *NF2*-related schwannomatosis based on clinical criteria without genetic analysis

» Genetic analysis with family history will be sufficient to diagnose *NF2*-related schwannomatosis (no requirement to have tumors)

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More information including a link to the 2021 and 2022 publications with updates to the diagnostic criteria for all types of neurofibromatosis and schwannomatosis can be found at **ctf.org/criteria**.

Learn more about all types of neurofibromatosis and schwannomatosis on the Children's Tumor Foundation website at: **ctf.org**

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DIAGNOSTIC CRITERIA FOR
LZTR1- AND *SMARCB1*-RELATED SCHWANNOMATOSIS

2022 UPDATE

CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH

LZTR1-RELATED SCHWANNOMATOSIS

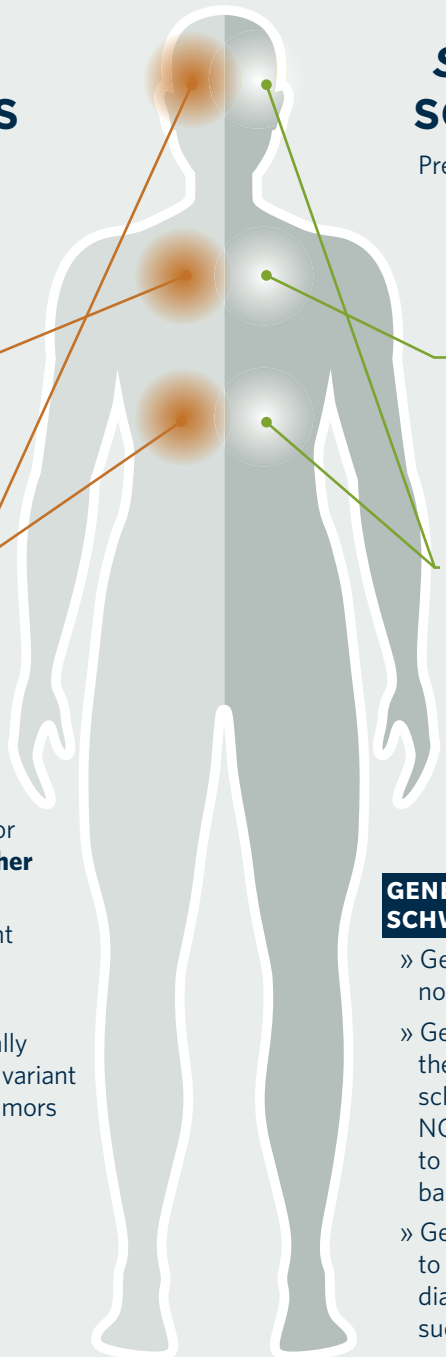
Previously classified as "schwannomatosis with *LZTR1* mutation"

A diagnosis of ***LZTR1*-related schwannomatosis** can be made when a patient meets **one of the following**:

» At least one pathologically confirmed schwannoma or hybrid nerve sheath tumor AND an *LZTR1* pathogenic variant in an unaffected tissue such as blood or saliva

» A common *LZTR1* pathogenic variant in two anatomically distinct schwannomas or hybrid nerve sheath tumors

Note: diagnosis requires surgical specimen to confirm tumor histology



SMARCB1-RELATED SCHWANNOMATOSIS

Previously classified as "schwannomatosis with *SMARCB1* mutation"

A diagnosis of ***SMARCB1*-related schwannomatosis** can be made when a patient meets **one of the following**:

» At least one pathologically confirmed schwannoma or hybrid nerve sheath tumor AND a *SMARCB1* pathogenic variant in an unaffected tissue such as blood or saliva

» A common *SMARCB1* pathogenic variant in two anatomically distinct schwannomas or hybrid nerve sheath tumors

Note: diagnosis requires surgical specimen to confirm tumor histology

Mosaicism

Mosaicism is confirmed for *LZTR1*-related or *SMARCB1*-related schwannomatosis by **either** of the following:

» Clearly less than 50% pathogenic variant allele fraction (VAF) in blood or saliva

OR

» Pathogenic variant not detected in clinically unaffected tissue but shared pathogenic variant in two or more anatomically unrelated tumors

GENETIC ANALYSIS FOR SCHWANNOMATOSIS:

» Genes involved with schwannomatosis are not yet fully understood

» Genetic analysis is REQUIRED for the diagnosis of a specific type of schwannomatosis (except for *NF2*-related, or NOS). In most cases, it will NOT be possible to diagnose the type of schwannomatosis based on clinical criteria alone

» Genetic analysis ALONE is not sufficient to diagnose all types of schwannomatosis; diagnosis also requires a clinical feature, such as schwannoma

CHILDREN'S TUMOR FOUNDATION
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DIAGNOSTIC CRITERIA FOR 22q-RELATED SCHWANNOMATOSIS

2022 UPDATE

CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH

22q-RELATED SCHWANNOMATOSIS

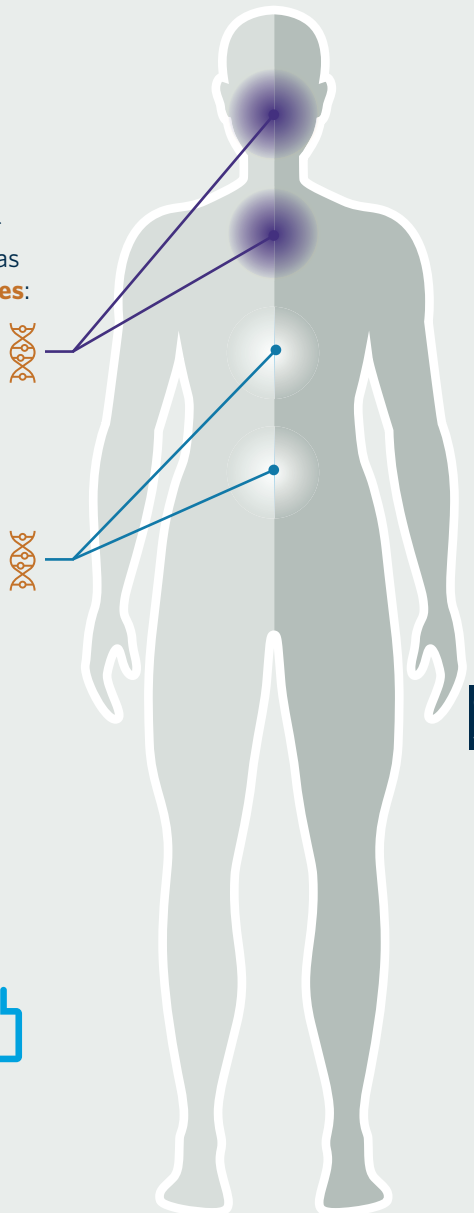
Previously classified as "schwannomatosis without identified mutation in blood" for patients with multiple schwannomas with common molecular findings on chromosome 22q

A diagnosis of **22q-related schwannomatosis** can be made when an individual does not meet criteria for *NF2*-related schwannomatosis, *SMARCB1*-related schwannomatosis, or *LTZR1*-related schwannomatosis, and has **both of the following molecular features**:

» Loss of heterozygosity (LOH) of the same chromosome 22q markers in two anatomically distinct schwannomas or hybrid nerve sheath tumors **AND**

» A different *NF2* pathogenic variant in each tumor which cannot be detected in unaffected tissue such as blood or saliva

Note: diagnosis requires **at least two** surgical specimens



GENETIC ANALYSIS FOR SCHWANNOMATOSIS:

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DIAGNOSTIC CRITERIA FOR
SCHWANNOMATOSIS-NOS (NOT OTHERWISE SPECIFIED) AND SCHWANNOMATOSIS-NEC (NOT ELSEWHERE CLASSIFIED)

2022 UPDATE

CHILDREN'S TUMOR FOUNDATION
ENDING NF THROUGH RESEARCH

SCHWANNOMATOSIS-NEC (Not Elsewhere Classified)

Previously classified as "schwannomatosis"

If genetic testing does not reveal pathogenic variant in known schwannomatosis-related genes, a diagnosis of **schwannomatosis-NEC** can be made if **both of the following criteria are met**:

» Presence of two or more lesions on appropriate imaging consistent with non-intradermal schwannomas

» At least one schwannoma or hybrid nerve sheath tumor is pathologically confirmed

Note: diagnosis requires surgical specimen to confirm tumor type

SCHWANNOMATOSIS-NOS (Not Otherwise Specified)

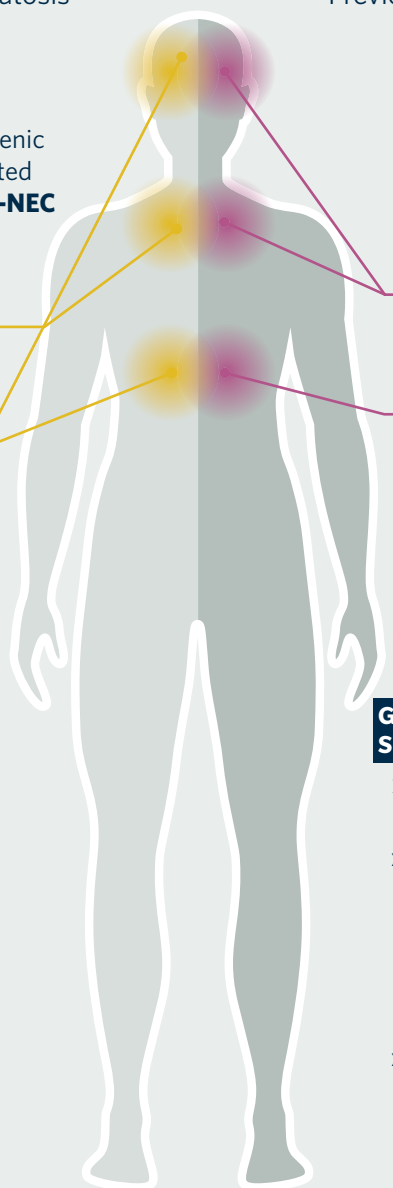
Previously classified as "schwannomatosis"

If genetic testing was not performed or is not available, a diagnosis of **schwannomatosis-NOS** can be made if **both of the following criteria are met**:

» Presence of two or more lesions on appropriate imaging consistent with non-intradermal schwannomas

» At least one schwannoma or hybrid nerve sheath tumor is pathologically confirmed

Note: diagnosis requires surgical specimen to confirm tumor type



GENETIC ANALYSIS FOR SCHWANNOMATOSIS:

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