



Neurofibromatosis type 2-related schwannomatosis: an update

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Abstract

Neurofibromatosis type 2-related schwannomatosis was first described in 1822. Although it is a different entity with a distinct presentation, it was initially confused with neurofibromatosis type 1 by our forefathers and continues to be confused by clinicians and patients today. Historically, physicians recognized that some patients presented earlier and had more severe phenotypes (Wishart versus Gardner). This has been better understood through genetic and molecular studies, which indicate that the differences are likely related to mosaicism rather than germline mutations. Recently, the nomenclature was changed to Neurofibromatosis type 2-related schwannomatosis, which is more appropriate. Diagnostic criteria have also been modified with the addition of genetic testing results. Treatment remains a conundrum. Historically, surgery has been the mainstay; however, it is risky for large tumors. Vascular endothelial growth factor inhibitors, such as bevacizumab, have been helpful in reducing the size of acoustic schwannomas and have been shown to preserve hearing, along with alleviating other symptoms. However, the medication has clear toxicities, and patients frequently become dependent on treatment or even develop tumor resistance. Numerous trials are ongoing to investigate reduced dosing regimens of vascular endothelial growth factor inhibitors and alternative molecular targets to determine whether the natural progression of the disease can be altered. Gene therapy is on the horizon.



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INTRODUCTION

History

Depictions of neurofibromatosis involving skin lesions were found even among ancient Egyptian findings dating back to 1500 BCE. That being said, most of these descriptions involve individuals with neurofibromatosis type 1 (NF1). It was not until 1777 that Eduard Sandifort, a professor of anatomy at the University of Leiden in the Netherlands, first described an acoustic neuroma at autopsy. Later, John H. Wishart, a Scottish surgeon and president of the Royal College of Surgeons in Edinburgh, described the clinical course and subsequent autopsy findings of Michael Blair. This individual succumbed at 21 years of age after developing progressive hearing loss, intractable headaches, and seizures. When Dr. Wishart performed the autopsy, he found multiple meningiomas and cranial nerve sheath tumors. Dr. Wishart provided the sentinel description of neurofibromatosis type 2-related schwannomatosis (NF2-related SWN) in 1822. Mossé and Cavalié first introduced the terms “peripheral” versus “central” neurofibromatosis in 1897^[1-5]. Despite differences in tumor locations and presentations, early physicians still considered these to be variations of the disease described by von Recklinghausen. In their 1940 writing, Dr. Gardner and Dr. Turner even referred to “an incomplete or abortive form of the disease”^[6,7].

In 1930, Gardiner and Frazier described a family in which 38 affected individuals suffered progressive hearing loss, progressive imbalance, and early demise. Autopsies on two of these individuals confirmed bilateral acoustic schwannomas. The physicians noted that about half of the family members were at risk for the condition, with no clear gender predilection or evidence of incomplete penetrance. Later reports, particularly by Moyes, suggested a completely independent autosomal dominant mutation, as most individuals did not classically follow the description by von Recklinghausen. NF2-related SWN was not considered an independent entity until 1970, when Dr. Young *et al.* provided an expanded description of the original 1930 family. By that point, there were 97 family members spanning nine generations. Affected family members had two or fewer small café au lait macules, and only two individuals had more than one subcutaneous nodule^[8-9].

These descriptions solidified the distinction between von Recklinghausen’s disease and “central” neurofibromatosis. Genetic linkage analysis localized the *NF2* gene to chromosome 22, in contrast to the *NF1* gene on chromosome 17^[10-12]. As such, in 1987, the National Institutes of Health formally named NF1 or “peripheral” and NF2 or “central” neurofibromatosis. It was in 1993 when the *NF2* tumor suppressor gene was identified on the long arm of chromosome 22^[13].

The *NF2* gene encodes the protein, merlin, which is related to the ezrin-radixin-moesin (ERM) family of proteins that link plasma membranes and actin filaments. It has widespread effects in the cell and regulates cell survival, proliferation, and cell-cell interactions in response to multiple pathways in the plasma membrane and the nucleus. Merlin inhibits downstream pathways of multiple receptor kinases, including epidermal growth factor (EGFR), vascular endothelial growth factor (VEGF), platelet-derived growth factor, and hepatocyte growth factor. The protein modulates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), rat sarcoma virus (Ras)/rapidly accelerated fibrosarcoma (Raf)/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), ras-related C3 botulinum toxin substrate (Rac)/p21-activated kinase (PAK), wntless-related integration site (Wnt), mammalian target of rapamycin (mTOR), yes-associated protein (YAP) and Hippo pathways. Merlin may also inhibit LIN28B in the nucleus, which would downregulate proto-oncogenic proteins such as MYC proto-oncogene, bHLH transcription factor (MYC)^[14,15].

Clinical findings

The average person sometimes develops symptoms between 18 and 24 years of age, related to neurological deficits^[16]. Almost all individuals are diagnosed with vestibular schwannomas by 30 years of age. Half present

with meningiomas, and about one-fourth have ependymomas^[16]. As opposed to NF1, astrocytomas are relatively rare. Vestibular schwannomas cause tinnitus, hearing loss and ataxia. Usually, hearing loss is progressive; however, it can occur suddenly. Schwannomas can develop on other cranial or peripheral nerves, but they tend to involve sensory rather than motor nerves. Spinal tumors can be schwannomas or ependymomas and multiple spinal tumors can be seen. Interestingly, many of the spinal tumors can be asymptomatic. Meningiomas are usually intracranial in the supratentorial compartment, but they can also be spinal. Intracranial meningiomas can lead to focal-onset epilepsy. If meningiomas are skull-based, they can lead to cranial neuropathy, brainstem compression and hydrocephalus. Adults can also develop mononeuropathy or polyneuropathy, even in the absence of nerve sheath tumors^[17,18].

NF2-related SWN is frequently unrecognized in childhood, when patients may present with intradermal skin lesions or ocular manifestations before developing or becoming symptomatic from intracranial tumors^[17]. Ocular findings include early-onset cataracts, retinal hamartomas, thickened optic nerves, CN3 palsies, epiretinal membranes, and retinal tufts on optical coherence tomography. Occasionally, a child may have a mononeuropathy without a tumor or an isolated meningioma or schwannoma. Cognitive impairment is not associated with NF2-related SWN^[18-24].

Historically, it has not been uncommon for individuals to progress to complete deafness. The average age of death is 36 years; however, due to the Gardner (milder) versus Wishart (more severe) phenotype, outcomes diverge. The Japanese Ministry of Health, Labor and Welfare maintains a National NF2 registry with a total of 807 patients, 44% male and 56% female. In their cohort, the age of onset ranged from less than 5 years to 80 years, exemplifying the wide variability in presentations. Patients who presented before 25 years of age had survival rates of 80%, 60%, and 28% at 5, 10, and 20 years, respectively. For patients who presented at 25 years of age or older, survival rates were 100%, 87%, and 62% at 5, 10, and 20 years, respectively^[18,19,20,25]. Clearly, the more symptomatic a person is, the earlier they present, and mortality is impacted.

Incidence and genetics

NF2-related SWN has an incidence of 1 in 25,000. It is an autosomal dominant disorder with 100% penetrance. In patients with de novo mutations, the vast majority exhibit somatic mosaicism^[26]. Studies estimate that about one-third of individuals with bilateral vestibular schwannomas, and up to 60% of those with a unilateral vestibular schwannoma, have mosaicism. For individuals with germline mutations, there is a 50% risk of passing the gene to a child; for those with somatic mosaicism, the risk is substantially lower (1 in 8 to 1 in 12 for individuals with negative *NF2* genetic testing). Children who present fulfilling clinical criteria likely have a more severe phenotype due to the presence of a germline mutation^[17,27].

UPDATES

Just as our forefathers were confused by the differences between NF1 and NF2-related SWN, confusion remains among some healthcare providers and patients or families. Some of this confusion was likely related to nomenclature. To address this conundrum, a consensus was developed to further distinguish these entities, leading to the formal recognition of NF1 and NF2-related SWN. International experts have since modified the clinical criteria and incorporated genetic and molecular data. See [Table 1](#)^[28].

Surgical and radiation treatment

Surgery has been the mainstay of therapy for vestibular schwannomas for many years. Small vestibular tumors (average size 1 cm, range 0-3 cm) can often be completely resected without compromising hearing or facial nerve function. Surgery becomes more challenging for larger tumors when the facial nerve is intact and hearing remains functional; in such cases, it may be reserved only for individuals with brainstem compression. Unfortunately, some patients may experience tumor recurrence or develop new tumors despite gross total resection. Gamma knife radiosurgery has been used and has gained prominence for the treatment

Table 1. Diagnostic Criteria for NF2-Related SWN

Diagnosis of NF2-related SWN with one of the following:	
<ul style="list-style-type: none"> • Bilateral vestibular schwannomas • Identical <i>NF2</i> pathogenic variant in at least 2 anatomically distinct NF2-related tumors (schwannoma, ependymoma, meningioma). If the mutation is found in < 50% of unaffected tissue, such as blood, then the diagnosis is mosaic NF2-related SWN 	
Either 2 major or 1 major and 2 minor criteria:	
Major	Minor
<ul style="list-style-type: none"> • Unilateral vestibular schwannoma • 1st-degree affected relative, other than sibling • 2 or more meningiomas • <i>NF2</i> pathogenic variant in unaffected tissue, such as blood (< 50% frequency indicates mosaicism) 	<ul style="list-style-type: none"> • Can count > 1 of a type: ependymoma, meningioma, dermal schwannoma • Can count only once: Juvenile subcapsular or cortical cataracts, retinal hamartoma, epiretinal membrane in a person < 40 years old, meningioma

NF2-related SWN: Neurofibromatosis type 2-related schwannomatosis.

of sporadic vestibular schwannomas; however, NF2-related schwannomas may not be as radiosensitive as their sporadic counterparts. Studies report long-term tumor control rates of 60%-80%, with hearing preservation in approximately 35% of patients. After treatment, patients have been noted to experience hearing decline or worsening cranial neuropathy, raising the question of whether these are treatment-related complications or disease progression despite therapy. Malignant transformation is uncommon but can occur up to 15 years after exposure; the risk has been estimated at 5%-6%, compared to less than 1% in those not treated with radiation^[29-34].

Pharmacological treatment

Bevacizumab (Genentech) is a recombinant humanized monoclonal antibody against VEGF and has been used for years in cancer therapy^[35]. In 2009, Plotkin *et al.* reported improved hearing in individuals with progressive vestibular schwannomas^[36]. This was later investigated in children and adolescents and was found to be beneficial for both hearing and tumor growth^[37]. Studies have confirmed diminished signal on diffusion tensor imaging and improved hearing with treatment. Bevacizumab has been associated with partial tumor volume reduction of 20% or more in approximately 40% of patients and disease stabilization in about half of cases. Only about 10% experience disease progression while on treatment. More importantly, 36% show hearing improvement, and 46% have hearing stabilization. Unfortunately, toxicity can occur, including thrombosis, hemorrhage, hypertension, proteinuria, colonic perforation, and menstrual disorders. To mitigate side effects, investigators have studied lower dosages; even regimens of 5 mg/kg or 2.5 mg/kg administered biweekly or triweekly have shown sustained response. The treatment can be tolerated for years, although rebound tumor growth has been reported once bevacizumab is withdrawn, despite good radiographic and audiological responses. Furthermore, bevacizumab was found to be helpful in eight patients with spinal ependymoma, all of whom experienced improvement in neurological symptoms, and half demonstrated radiographic response to treatment^[38-42].

DNA methylation studies have been performed. Shi *et al.* demonstrated that NF2-related vestibular schwannomas exhibit both hyper- and hypo-methylated sequences, corresponding to areas of over- and under-expression. Highly expressed genes promoted innate immune responses, gene expression, and cell migration. Low-expression genes appeared to regulate RNA polymerase II promoters, embryonic limb morphogenesis, fat cell differentiation, and MAPK pathway upregulation. Significantly enriched pathways included PI3K/Akt, MAPK, Ras, and cell adhesion molecule signaling^[43]. Tsuchiya *et al.* highlighted the wide array of mutations across sporadic and NF2-related vestibular schwannomas. They emphasized the importance of the tumor microenvironment, including inflammation and heterogeneity, and suggested that a better understanding could provide insights into treatment and management^[44]. In summary, targeted therapy may be beneficial for some patients, at least temporarily; however, it is not universally effective, and cytotoxic regimens have generally been unsuccessful.

In 2013, tyrosine kinase inhibition through ALK-IN-1 appeared to be helpful in preclinical models of NF2-deficient schwannomas and meningiomas. Subsequent trials of brigatinib showed inhibitory activity in mouse models of NF2-related nonvestibular schwannomas and meningiomas^[45]. The drug was then evaluated in a clinical trial through the Innovative Trial for Understanding the Impact of Targeted Therapies in NF2 (INTUITT-NF2) Consortium. This phase 2 trial included patients aged 12 years and older, involved 40 participants, and had a 10-month follow-up. Brigatinib not only alleviated clinical symptoms but also demonstrated radiographic responses in target tumors and other tumors. Interestingly, the meningiomas appeared to respond best to the treatment. The study is ongoing to monitor response, but it is no longer recruiting patients^[46].

Other tyrosine kinase inhibitors are being investigated through open clinical trials, including crizotinib (NCT04283669). Lapatinib, a tyrosine kinase inhibitor of EGFR, demonstrated an objective response in 4 of 17 progressive vestibular schwannomas; however, erlotinib was not effective in 11 patients^[47,48]. Due to activation of the AKT/PI3K pathway, histone deacetylase (HDAC) inhibitors are also being investigated, such as REC-2282 (NCT05130866). The mTOR inhibitors have shown some activity in NF2-related tumors^[49,50]. A trial combining valproic acid (HDAC inhibitor) with bevacizumab and temsirolimus (NCT01552434) is open and actively recruiting patients.

The MEK enzymes are activated in NF2-related schwannomatosis and NF1. MEK inhibitors have been a game-changer in NF1-related plexiform neurofibromas and are now approved by the U.S. Food and Drug Administration (FDA) for children 2 years of age and older (NCT01362803)^[51,52]. Treatment with mirdametinib has also been approved by the FDA for both adults and children^[53-55]. NCT03095248 investigated selumetinib in NF2-related tumors; the study is complete, but no results have been posted or reported.

In preclinical studies, other inhibitors are being investigated, such as pictilisib, a pan-PI3K inhibitor, and PF-3758309, a PAK inhibitor. Combination treatment demonstrated cell cycle arrest and apoptosis in merlin-deficient mouse Schwann cells and cell cycle arrest in merlin-deficient human Schwann cells^[56].

Gene therapy

Finally, gene therapy has changed the course of numerous disease entities, including spinal muscular atrophy and Duchenne Muscular Dystrophy^[57-62]. It is now being investigated in NF1 mouse models and will be the future of all genetic syndromes, including NF2-related SWN. Prabhakar *et al.* published encouraging findings of using adenoviral vectors [adeno-associated virus (AAV1)-constitutive chicken β -actin (CBA)-FLAG-merlin] to introduce the NF2 into cultured merlin-negative arachnoidal and schwann cells. They demonstrated the ability for the cells to generate merlin, down-regulate mammalian target of rapamycin complex (mTORC) and size normalization of the cells. The investigators then introduced human schwannomas into the sciatic nerves of nude mice and monitored tumor growth. They injected the tumors once with the same AAV1-CBA-FLAG-merlin vector and observed the mice over a 10-week period. Seven of nine tumors regressed, one remained stable, and one progressed despite treatment. The mice did not appear to experience treatment-related toxicity. When the tumors were harvested, some atypical cells and areas of hypercellularity were noted; however, there was clear tumor regression, and Ki67 staining provided further encouraging results^[63]. Others are also studying non-viral vectors, which are more economical and have lower immunogenicity and mutagenesis^[64].

CONCLUSION

In summary, significant progress has been made in understanding NF2-related SWN. The clinical presentation and genetic findings have been well described, facilitating appropriate diagnosis for clinicians. The main remaining challenge is differentiating NF2-related SWN from non-NF2-related SWN and

understanding the overlap between them. The modified nomenclature facilitates clearer distinctions between NF1- and NF2-related SWN. It is clear that surgery is not the mainstay of treatment for schwannomatosis. Collateral damage to nerve function, along with musculoskeletal and cosmetic complications, frequently occurs, making systemic treatment essential. Investigators are actively studying sporadic vestibular schwannomas, NF2-related vestibular schwannomas, and schwannomas at other sites to better understand tumorigenesis and to expand treatment paradigms. Targeted treatments are now available but remain limited. An important question is whether targeted therapies in combination would be more effective. Gene therapy is also being actively investigated. It is only a matter of time before these treatments and approaches are extended to patients with NF2-related SWN and eventually to those with non-NF2-related SWN. The natural history of the disease is evolving before our eyes, and patients and their families have reason for hope.

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The author contributed solely to the article.

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REFERENCES

1. Ahn MS, Jackler RK, Lustig LR. The early history of the neurofibromatoses: evolution of the concept of neurofibromatosis type 2. *Arch Otolaryngol Head Neck Surg.* 1996;122:1240-9. DOI PubMed
2. Brosius S. A history of von Recklinghausen's NF1. *J Hist Neurosci.* 2010;19:333-48. DOI PubMed
3. Huson SM, Hughes RAC. The neurofibromatoses: a pathogenetic and clinical overview. Chapman & Hall Medical; 1994. <https://archive.org/details/neurofibromatose0000unse>. [Last accessed on 7 Jan 2026].
4. Mossé A, Cavalié . Tumeurs multiples de l'encephale et de la moelle allongée: neurofibromatosis centrale. *Gaz Hebd Med Chir.* 1897;2:789.
5. Ruggieri M, Praticò AD, Serra A, et al. Early history of neurofibromatosis type 2 and related forms: earliest descriptions of acoustic neuromas, medical curiosities, misconceptions, landmarks and the pioneers behind the eponyms. *Childs Nerv Syst.* 2017;33:549-60. DOI
6. Gardner WJ, Turner O. Bilateral acoustic neurofibromas: further clinical and pathologic data on hereditary deafness and Recklinghausen's disease. *Arch Neurol Psychiatry.* ;1940, 44(1):76-99. DOI
7. Gardner WJ, Frazier CH. Bilateral acoustic neurofibromas: a clinical study and field survey of a family of five generations with bilateral deafness in thirty-eight members. *Arch Neurol Psychiatry.* 1930;23:266-302. DOI
8. Moyes PD. Familial bilateral acoustic neuroma affecting 14 members from four generations. *J Neurosurg.* 1968;29:78-82. DOI
9. Young DF, Eldridge R, Gardner WJ. Bilateral acoustic neuroma in a large kindred. *JAMA.* 1970;214:347-53. DOI
10. Seizinger BR, Martuza RL, Gusella JF. Loss of genes on chromosome 22 in tumorigenesis of human acoustic neuroma. *Nature.* 1986;322:644-7. DOI PubMed

11. Rouleau GA, Merel P, Lutchman M, et al. Alteration in a new gene encoding a putative membrane-organizing protein causes neurofibromatosis type 2. *Nature*. 1993;363:515-21. [DOI](#)
12. Barker D, Wright E, Nguyen K, et al. Gene for von Recklinghausen neurofibromatosis is in the pericentromeric region of chromosome 17. *Science*. 1987;236:1100-2. [DOI](#)
13. Trofatter JA, MacCollin MM, Rutter JL, et al. A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. *Cell*. 1993;72:791-800. [DOI](#)
14. Hiruta R, Saito K, Bakhit M, Fujii M. Current progress in genomics and targeted therapies for neurofibromatosis type 2. *Fukushima J Med Sci*. 2023;69:95-103. [DOI PubMed PMC](#)
15. Ghalavand MA, Asghari A, Farhadi M, Taghizadeh-Hesary F, Garshasbi M, Falah M. The genetic landscape and possible therapeutics of neurofibromatosis type 2. *Cancer Cell Int*. 2023;23:99. [DOI PubMed PMC](#)
16. Emanuel BS, Zackai EH, Medne L. Emanuel Syndrome. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1263/> [Last accessed on 11 Oct 2025].
17. Sperfeld AD, Hein C, Schröder JM, Ludolph AC, Hanemann CO. Occurrence and characterization of peripheral nerve involvement in neurofibromatosis type 2. *Brain*. 2002;125:996-1004. [DOI](#)
18. Hexter A, Jones A, Joe H, et al. Clinical and molecular predictors of mortality in neurofibromatosis 2: a UK national analysis of 1192 patients. *J Med Genet*. 2015;52:699-705. [DOI](#)
19. Forde C, King AT, Rutherford SA, et al. Disease course of neurofibromatosis type 2: a 30-year follow-up study of 353 patients seen at a single institution. *Neuro Oncol*. 2021;23:1113-24. [DOI PubMed PMC](#)
20. Evans DG, Birch JM, Ramsden RT. Paediatric presentation of type 2 neurofibromatosis. *Arch Dis Child*. 1999;81:496-9. [DOI PubMed PMC](#)
21. Feucht M, Griffiths B, Niemüller I, et al. Neurofibromatosis 2 leads to higher incidence of strabismological and neuro-ophthalmological disorders. *Acta Ophthalmol*. 2008;86:882-6. [DOI](#)
22. Ruggieri M, Iannetti P, Polizzi A, et al. Earliest clinical manifestations and natural history of neurofibromatosis type 2 (NF2) in childhood: a study of 24 patients. *Neuropediatrics*. 2005;36:21-34. [DOI](#)
23. Pathmanaban ON, Sadler KV, Kamaly-Asl ID, et al. Association of genetic predisposition with solitary schwannoma or meningioma in children and young adults. *JAMA Neurol*. 2017;74:1123-9. [DOI PubMed PMC](#)
24. Halliday D, Emmanouil B, Evans DG. Updated protocol for genetic testing, screening and clinical management of individuals at-risk of NF2-related schwannomatosis. *Clin Genet*. 2023;103:540-52. [DOI PubMed](#)
25. Halliday D, Parry A, Evans DG. Neurofibromatosis type 2 and related disorders. *Curr Opin Oncol*. 2019;31:562-7. [DOI](#)
26. Evans DG, Moran A, King A, Saeed S, Gurusinghe N, Ramsden R. Incidence of vestibular schwannoma and neurofibromatosis 2 in the North West of England over a 10-year period: higher incidence than previously thought. *Otol Neurotol*. 2005;26:93-7. [DOI](#)
27. 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*. 2007;44:424-8. [DOI PubMed PMC](#)
28. Plotkin SR, Messiaen L, Legius E, et al.; International Consensus Group on Neurofibromatosis Diagnostic Criteria (I-NF-DC). Updated diagnostic criteria and nomenclature for neurofibromatosis type 2 and schwannomatosis: an international consensus recommendation. *Genet Med*. 2022;24:1967-7. [DOI PubMed](#)
29. Jiramongkolchai P, Schwartz MS, Friedman RA. Management of Neurofibromatosis Type 2-Associated Vestibular Schwannomas. *Otolaryngol Clin North Am*. 2023;56:533-41. [DOI PubMed](#)
30. Rowe JG, Radatz MW, Walton L, Soanes T, Rodgers J, Kemeny AA. Clinical experience with gamma knife stereotactic radiosurgery in the management of vestibular schwannomas secondary to type 2 neurofibromatosis. *J Neurol Neurosurg Psychiatry*. 2003;74:1288-93. [DOI PubMed PMC](#)
31. Tosi U, Maayan O, An A, et al. Stereotactic radiosurgery for vestibular schwannomas in neurofibromatosis type 2 patients: a systematic review and meta-analysis. *J Neurooncol*. 2022;156:431-41. [DOI](#)
32. Puataweepong P, Dhanacha M, Ruangkanchanasetr R, et al. Long-term clinical outcomes of stereotactic radiotherapy for bilateral vestibular schwannomas in neurofibromatosis type 2 patients. *J Neurooncol*. 2023;164:587-95. [DOI](#)
33. Bin-Alamer O, Faramand A, Alarifi NA, et al. Stereotactic radiosurgery for vestibular schwannoma in neurofibromatosis type 2: an international multicenter case series of response and malignant transformation risk. *Neurosurgery*. 2023;92:934-44. [DOI](#)
34. Evans DG, Halliday D, Obholzer R, et al.; English Specialist NF2 Research Group. Radiation treatment of benign tumors in NF2-related-schwannomatosis: A national study of 266 irradiated patients showing a significant increase in malignancy/malignant progression. *Neurooncol Adv*. 2023;5:vdad025. [DOI PubMed PMC](#)
35. Ferrara N, Hillan KJ, Gerber H-P, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat Rev Drug Discov*. 2004;3:391-400. [DOI PubMed](#)

36. Plotkin SR, Stemmer-Rachamimov AO, Barker FG, et al. Hearing improvement after bevacizumab in patients with neurofibromatosis type 2. *N Engl J Med.* 2009;361:358-67. [DOI PubMed PMC](#)
37. Plotkin SR, Allen J, Dhall G, et al. Multicenter, prospective, phase II study of maintenance bevacizumab for children and adults with NF2-related schwannomatosis and progressive vestibular schwannoma. *Neuro Oncol.* 2023;25:1498-506. [DOI](#)
38. Farschtschi S, Kollmann P, Dalchow C, Stein A, Mautner VF. Reduced dosage of bevacizumab in treatment of vestibular schwannomas in patients with neurofibromatosis type 2. *Eur Arch Otorhinolaryngol.* 2015;272:3857-60. [DOI](#)
39. Screnci M, Puechmaille M, Berton Q, Khalil T, Mom T, Coll G. Bevacizumab for Vestibular Schwannomas in Neurofibromatosis Type 2: A Systematic Review of Tumor Control and Hearing Preservation. *J Clin Med.* 2024;13:7488. [DOI PubMed PMC](#)
40. Renzi S, Michaeli O, Salvador H, et al. Bevacizumab for NF2-associated vestibular schwannomas of childhood and adolescence. *Pediatr Blood Cancer.* 2020;67:e28228. [DOI](#)
41. Webb MJ, Neth BJ, Webb LM, et al. Withdrawal of bevacizumab is associated with rebound growth of vestibular schwannomas in neurofibromatosis type 2-related schwannomatosis patients. *Neuro Oncol Adv.* 2023;5:vdad123. [DOI PubMed PMC](#)
42. Farschtschi S, Merker VL, Wolf D, et al. Bevacizumab treatment for symptomatic spinal ependymomas in neurofibromatosis type 2. *Acta Neurol Scand.* 2016;133:475-80. [DOI](#)
43. Shi J, Lu D, Gu R, et al. Integrated analysis of transcriptome and differential methylation of neurofibromatosis type 2 vestibular schwannomas. *World Neurosurg.* 2022;157:e66-e76. [DOI](#)
44. Tsuchiya T, Miyawaki S, Teranishi Y, et al. Current molecular understanding of central nervous system schwannomas. *Acta Neuropathol Commun.* 2025;13:24. [DOI PubMed PMC](#)
45. Chang LS, Oblinger JL, Smith AE, et al.; Synodos for NF2 Consortium. Brigatinib causes tumor shrinkage in both NF2-deficient meningioma and schwannoma through inhibition of multiple tyrosine kinases but not ALK. *PLoS One.* 2021;16:e0252048. [DOI PubMed PMC](#)
46. Plotkin SR, Yohay KH, Nghiemphu PL, et al.; INTUITT-NF2 Consortium. Brigatinib in NF2-related schwannomatosis with progressive tumors. *N Engl J Med.* 2024;390:2284-94. [DOI](#)
47. Karajannis MA, Legault G, Hagiwara M, et al. Phase II trial of lapatinib in adult and pediatric patients with neurofibromatosis type 2 and progressive vestibular schwannomas. *Neuro Oncol.* 2012;14:1163-70. [DOI PubMed PMC](#)
48. Plotkin SR, Halpin C, McKenna MJ, et al. Erlotinib for progressive vestibular schwannoma in neurofibromatosis 2 patients. *Neuro Oncol.* 2010;31:1135-43. [DOI](#)
49. Goutagny S, Raymond E, Esposito-Farese M, et al. Phase II study of mTORC1 inhibition by everolimus in neurofibromatosis type 2 patients with growing vestibular schwannomas. *J Neurooncol.* 2015;122:313-20. [DOI](#)
50. Karajannis MA, Legault G, Hagiwara M, et al. Phase II study of everolimus in children and adults with neurofibromatosis type 2 and progressive vestibular schwannomas. *Neuro Oncol.* 2014;16:292-7. [DOI PubMed PMC](#)
51. Dombi E, Baldwin A, Marcus LJ, et al. Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. *N Engl J Med.* 2016;375:2550-60. [DOI](#)
52. Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. *N Engl J Med.* 2020;382:1430-42. [DOI](#)
53. Weiss BD, Wolters PL, Plotkin SR, et al. NF106: a neurofibromatosis clinical trials consortium phase II trial of the MEK inhibitor mirdametinib (PD-0325901) in adolescents and adults with NF1-RELATED PLEXIFORM NEUROFIBROMAS. *J Clin Oncol.* 2021;39:797-806. [DOI](#)
54. Moertel CL, Hirbe AC, Shuhaiber HH, et al.; ReNeu Trial Investigators. ReNeu: a pivotal, phase iib trial of mirdametinib in adults and children with symptomatic neurofibromatosis type 1-associated plexiform neurofibroma. *J Clin Oncol.* 2025;43:716-29. [DOI PubMed PMC](#)
55. Hoy SM. Correction: mirdametinib: first approval. *Drugs.* 2025;85:1079. [DOI PubMed PMC](#)
56. Nagel A, Huegel J, Petrilli A, et al. Simultaneous inhibition of PI3K and PAK in preclinical models of neurofibromatosis type 2-related schwannomatosis. *Oncogene.* 2024;43:921-30. [DOI PubMed PMC](#)
57. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med.* 2017;377:1713-22. [DOI](#)
58. Nishio H, Niba ETE, Saito T, Okamoto K, Takeshima Y, Awano H. Spinal muscular atrophy: the past, present, and future of diagnosis and treatment. *Int J Mol Sci.* 2023;24:11939. [DOI PubMed PMC](#)
59. Hoy SM. Onasemnogene abeparvovec: first global approval. *Drugs.* 2019;79:1255-62. [DOI PubMed](#)
60. Le Guiner C, Servais L, Montus M, et al. Long-term microdystrophin gene therapy is effective in a canine model of Duchenne muscular dystrophy. *Nat Commun.* 2017;8:16105. [DOI PubMed PMC](#)
61. Abdul-Razak H, Malerba A, Dickson G. Advances in gene therapy for muscular dystrophies. *F1000Res.* 2016;5:2030. [DOI PubMed PMC](#)

-
62. Elangkovan N, Dickson G. Gene Therapy for Duchenne Muscular Dystrophy. *J Neuromuscul Dis.* 2021;8:S303-16. [DOI PubMed PMC](#)
 63. Prabhakar S, Beauchamp RL, Cheah PS, et al. Gene replacement therapy in a schwannoma mouse model of neurofibromatosis type 2. *Mol Ther Methods Clin Dev.* 2022;26:169-80. [DOI PubMed PMC](#)
 64. Yuan R, Wang B, Wang Y, Liu P. Gene therapy for neurofibromatosis type 2-related schwannomatosis: recent progress, challenges, and future directions. *Oncol Ther.* 2024;12:257-76. [DOI](#)

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