The Turkish Journal of Pediatrics 2025; 67: 611-622
https://doi.org/10.24953/turkjpediatr.2025.6461

Review

Neurofibromatosis type 1-associated tumors in children

Hilal Susam Şen[1]

[1]*Division of Pediatric Oncology, Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara, Türkiye.*

ABSTRACT

Neurofibromatosis type 1 (NF1) is characterized by the involvement of multiple systems, including dermatological, neurological, skeletal, and cognitive manifestations. NF1 exhibits almost complete penetrance, with a wide range of symptoms that usually develop over the course of a person's lifetime. The most obvious signs are café-au-lait macules, neurofibromas and axillary or inguinal freckling.Patients with NF1 are predisposed to developing benign and malignant tumors. Some of these tumors are exhibited during childhood. The rate of cancer development over a person's lifetime is higher for patients with NF1 than for the general population. Malignancies associated with NF1 include low grade gliomas, malignant peripheral nerve sheath tumors, juvenile myelomonocytic leukemias, pheochromocytomas, gastrointestinal stromal tumors, rhabdomyosarcomas, breast cancers, malignant melanomas, acute lymphoblastic leukemias, non-Hodgkin lymphomas, carcinoid tumors, and Wilms tumors. The identification of patients with NF1 and their interittent follow-up are important for the early detection of potential complications, especially tumorigenesis. This review aimed to summarize NF1-associated tumors in pediatric patients and recently developed targeted therapies for treating these tumors.

Key words: child, neurofibromatosis type 1, neoplasms, *NF1* gene.

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous syndrome resulting from mutations in the NF1 gene found on chromosome 17q11.2. The involvement of multiple systems is a characteristic feature, with manifestations occurring in the dermatological, neurological, skeletal and cognitive functions. . Approximately one in 3,000 people across the globe are affected by NF1, with no difference in terms of ethnicity or sex.[1] De novo mutations account for around 50% of cases, while the remaining 50% are inherited in an autosomal dominant manner.[2] NF1 exhibits almost complete penetrance, with a wide range of symptoms that usually develop over the course of a person's lifetime.[2] The most obvious signs are café-au-lait macules, neurofibromas and axillary or inguinal freckling.[3] Although café-au-lait macules are the most common symptom of NF1, the presence of café-au-lait macules alone may also be seen in other genetic disorders such as constitutional mismatch repair deficiency syndrome, McCune-Albright Syndrome, Legius syndrome, multiple familial café-au-lait, Cowden syndrome, and Leopard/multiple lentigenes syndrome.[4] A number of other systemic complications have been identified, including optic pathway gliomas and skeletal abnormalities. There is also an increased risk of malignancy. The variability in phenotype emphasises the importance of a personalized approach to diagnosis and treatment. This is crucial for ensuring effective treatment and improving patients' quality of life. The revised 2021 guidelines state that a diagnosis of NF1 can be made if an individual exhibits two or more of the following manifestations:

✉ Hilal Susam Şen ▪ hilalsusam@hotmail.com

Received 23rd Jun 2025, revised 12th Aug 2025, accepted 29th Aug 2025.

a. Six or more café-au-lait macules (greater than 5mm in pre-pubertal children or greater than 15 mm in post-pubertal individuals).

b. Freckling in the axilla (armpit) or groin.

c. Two or more neurofibromas of any type, or one plexiform neurofibroma.

d. Two or more Lisch nodules or two or more choroidal abnormalities.

e. Optic pathway glioma.

f. A distinctive osseous lesion such as sphenoid dysplasia; anterolateral bowing of tibia (tibial dysplasia) or pseudarthrosis of a long bone.

g. A pathogenic *NF1* gene variant, or a first-degree relative meeting diagnostic criteria.[1]

Neurofibromin, which is primarily found in neurons, Schwann cells and glial cells, is a large, multifunctional protein that is encoded by the tumor suppressor gene *NF1*.[3] Neurofibromin is involved in several cell signaling pathways, including the Ras/MAPK, Akt/mTOR, and cAMP/PKA pathways, and regulates many cellular processes. The loss of neurofibromin results in uncontrolled cell proliferation, leading to tumor development associated with NF1.[3] Patients with NF1 are predisposed to developing benign and malignant tumors. The lifetime cancer development rate in patients with NF1 is increased compared to the normal population. Table I shows the cancers associated with NF1. The identification of patients with NF1 and their intermittent follow-up are important for the early detection of potential complications, especially tumorigenesis. This review aimed to summarize NF1-associated tumors in pediatric patients and recently developed targeted therapies for treating these tumors.

Cutaneous Neurofibroma and Plexiform Neurofibroma (PN)

The presence of cutaneous neurofibromas on the face and limbs can cause distress and social anxiety. Their raised appearance can cause itching or pain, and friction or pressure from clothing when moving around.It is estimated that 20–50% of patients with NF1 will develop PN, which may appear at birth or during the first few years of life, localizing to the craniofacial, paraspinal, mediastinal, extremities, and retroperitoneal regions, leading to significant complications. Congenital ones, in particular, gradually enlarge and feel worm-like when palpated. Additionally, PN exhibits progression along the nerve trunk. Among patients with PN, 8%–12% develop malignant peripheral nerve sheath tumors (MPNSTs).[5] A careful examination is needed to check for PN in all individuals with NF1. This should be followed by monitoring to detect any growth of PN. . A standard evaluation includes a medical history, physical and neurological examination.[5] The symptoms of PNs include pain, facial disfigurement, neurological deficits, deformities, orthopedic problems, and airway obstruction. Although PNs are benign tumors, treatment may be necessary due to their location and the resulting morbidity and functional

Table I. NF1-related malignancies

Strongly associated malignancies	Possibly related malignancies
Low grade gliomas	Breast cancer
Malignant peripheral nerve sheath tumor	Malignant melanoma
Juvenile myelomonocytic leukemia	Acute lymphoblastic leukemia
Pheochromocytoma	Non-Hodgkin lymphoma
Gastrointestinal stromal tumor	Carcinoid tumor
Rhabdomyosarcoma	Wilms tumor

NF1: neurofibromatosis type 1

impairment.[6] The goal of treatment is usually to improve or prevent PN-associated morbidity. The presence of morbidity, especially when it does not respond to symptomatic treatment, is of paramount importance. The preferred therapeutic strategy for PNs is total surgical excision if the surgery can be performed without causing morbidity.[7] Most superficial PNs can be surgically excised, alleviating the symptoms. However, most patients are not eligible for surgery as the tumor is located deeply along the nerve tract. Most patients undergoing subtotal excision exhibit PN progression. The discovery of the molecular pathogenesis and the biological basis of this disorder has enabled the development of targeted therapies. In the last two decades, clinical trials have evaluated the therapeutic efficacy of imatinib, sirolimus, tipifarnib, pirfenidone, peginterferon, trametinib, cabozantinib, and selumetinib in NF1-associated PN.[8-16] Selumetinib treatment resulted in a 70% reduction in pain and a reduction in tumor size of between 30% and 50%.[15] However, Food and Drug Administration (FDA)-approved drugs were not available for PNs until recently. MAPK (mitogen-activated protein kinase) kinase (MEK) inhibition is an effective treatment strategy for PN. In April 2020, the FDA approved selumetinib, an oral MEK-1/2 inhibitor, for treating symptomatic and inoperable PN in pediatric patients with NF1 aged ≥ 2 years. Additionally, the MEK inhibitor mirdametinib has been reported to exert therapeutic effects on PN[17] and was approved by the FDA in February 2025 for the treatment of pediatric patients (aged ≥ 2 years) with symptomatic and inoperable PN. The results of clinical trials demonstrated that mirdametinib effectively reduced the size of PNs by 41–52% in both adult and pediatric patients.[17] Studies evaluating the efficacy of MEK inhibitors in PN are summarized in Table II.

Malignant Peripheral Nerve Sheath Tumor (MPNST)

MPNST is an aggressive spindle cell sarcoma that arises from peripheral nerve sheath cells. It is one of the most common non-rhabdomyosarcoma soft tissue sarcomas in children. The incidence rate of MPNST is rare, but MPNST has been diagnosed in 20% to 50% of patients with NF1.[18] In around half of the cases, MPNST develops on the basis of a pre-existing PN. Compared to other non-rhabdomyosarcoma soft tissue sarcomas, MPNST has particular characteristics. For example, it often arises at axial sites, such as the trunk and head–neck region, while most other non-rhabdomyosarcoma soft tissue sarcomas generally develop in the extremities. MPNST also shows marked local invasiveness. In recent years, the main international pediatric sarcoma cooperative groups have published two prospective protocols specifically designed for non-rhabdomyosarcoma soft tissue sarcomas[19,20], and have defined the current risk-adapted multimodal standards of care for non-rhabdomyosarcoma soft tissue sarcomas.

Table II. Efficacy of MEK inhibitors in children with NF1 and PN

MEK inhibitor	NCT Number	Phase	>20% decrease from baseline PN volume
Selumetinib	NCT01362803	1	17/24 (71%)
	NCT01362803	2	34/50 (68%)
Mirdametinib	NCT02096471	2	8/19 (42%)
	NCT03962543	2	7/20 (35%)
Cabozantinib	NCT02101736	2	8/19 (42%)
Trametinib	NCT02124772	1/2	12/26 (46%)
Binimetinib	NCT03231306	2	13/20 (65%)

Adapted from Armstrong et al.[6]
MEK: mitogen-activated protein kinase kinase, NCT: national clinical trial, NF1: neurofibromatosis type 1, PN: plexiform neurofibroma.

The presentations of MPNST are pain, bleeding and rapid growth by 20% of a previously known PN. The magnetic resonance imaging (MRI) and positron emission tomography – computerized tomography (PET-CT) results support the suspicion of conversion to MPNST. MPNST is an aggressive, fatal disease with an overall survival rate of 20%–40%.[21] Total surgical excision is the preferred treatment for MPNST as the tumor is chemoresistant. R0 resection is important for improving survival rates. However, adequate surgery is often not possible for deep tumors that extend to adjacent structures. The involvement of major nerves, which is typical of MPNST, often makes the tumor unresectable. The lack of local control is generally reported as the main cause of treatment failure, which can have a considerable effect on patient outcomes. The role of radiotherapy in MPNST is controversial, especially for pediatric patients. Potential side effects must be considered before using radiotherapy. Although radiotherapy is used to provide local control in MPNST, its effect on overall survival has not been demonstrated. If radiotherapy is unavoidable, it is essential to limit the total dose and field size. For NF1 patients who require radiation therapy and are not limited by financial constraints, proton beam therapy is a sensible option.[22] Proton therapy reduces the dose to organs at risk, making a lower integral dose achievable.[23] Given the critical locations of MPNSTs and the young age of patients, proton therapy seems an appropriate treatment strategy in order to ensure local control for this group. A recent series by Ferrari et al. suggests that a combined local treatment that included both surgical resection and radiotherapy could improve local control.[24] Systemic chemotherapy could be considered as the primary medical treatment. In most cases, systemic chemotherapy formed part of the treatment scheme. Patients with high-grade tumors larger than 5 cm generally received adjuvant chemotherapy after initial R0/R1 resection.[24] Chemotherapy protocols, including ifosfamide and adriamycin, are preferred in non-metastatic and metastatic cases.[25]

The potential therapeutic targets for MPNST include receptor kinases, the MAPK pathway, and the phosphoinositide 3-kinase – protein kinase B – mammalian target of rapamycin (PI3K-AKT-mTOR) pathway. These targets are present at all three levels of physiological signal transduction. Similar to PN, MAPK pathway inhibition with MEK inhibitors is a therapeutic strategy for NF1-associated MPNST. The FDA has not approved selumetinib for the treatment of MPNST. However, studies are ongoing to evaluate the efficacy of MEK inhibitors in PN and MPNST (NCT03433183 and NCT02124772). The use of MEK inhibitors is not recommended as a standalone treatment. The SARC031 study (NCT03433183) examined the efficacy of the combination of selumetinib and the mTOR inhibitor sirolimus in patients with nonresectable or metastatic MPNST. Positron emission tomography-computed tomography scans revealed that this combination achieved partial metabolic responses but did not translate into treatment success.[26]

Targeting tyrosine kinase receptors alone or in combination with chemotherapy may inactivate the MAPK or mTOR pathways. In a randomized phase 2 trial, the event-free survival rate in patients treated with doxorubicin and olaratumab (an anti-platelet-derived growth factor receptor alpha antibody) combination therapy was higher than that in patients treated with doxorubicin monotherapy.[27] Receptor tyrosine kinase inhibitors, such as erlotinib, sunitinib, sorafenib, cediranib, and dasatinib, can exert growth-inhibitory effects on NF1-related tumors. However, several phase I trials have reported that receptor tyrosine kinase inhibitors are ineffective. Limited studies have evaluated the efficacy of receptor tyrosine kinase inhibitors for NF1-related tumors.[28-33] Additionally, receptor tyrosine kinase inhibitors are associated with several side effects. In a study on 25 adult patients with MPNST, only three patients achieved stable disease with the combination therapy of everolimus and bevacizumab.[34] Anti-programmed cell death-1 ligand 1 (PD[L]-1) inhibitors, which are a type

of immunotherapy, are effective in treating various cancers, including melanoma, non-small cell lung cancer, and mesothelioma. One study investigating the effect of pembrolizumab on MPNSTs is currently ongoing (NCT02691026). Oncolytic viruses are reported to be effective in vivo. One study is investigating the effects of the oncolytic measles virus on patients with MPNST (NCT02700230).

Optic Pathway Glioma and Low Grade Glioma

Optic pathway glioma (OPG)

OPGs, which are the predominant pilocytic astrocytomas, are typically diagnosed within the first decade of life. OPGs affect the axons of the visual pathway and may affect the optic nerve, optic chiasm, optic tracts, optic radiation and hypothalamus individually or in combination. Children without a known OPG should undergo annual vision screening until the age of eight, and then every two years until the age of 18, since vision loss is less common in older age groups.[35,36] Routine MRI follow-up is not recommended if there are no visual symptoms.[36] The standard imaging modality for OPGs is an MRI scan of the brain and orbit.[37,38] Children with NF1 who experience unexplained vision loss or new-onset optic nerve pallor should undergo an MRI scan to evaluate their visual pathways. Although OPGs are asymptomatic, they may present with visual complaints or endocrinological aberrations.[39] It can be difficult for parents to recognise deterioration of vision in a young child, and it can often go unnoticed. The symptoms vary depending on where the tumor is located. Those confined to the optic nerve usually present with decreased visual acuity. Other symptoms include loss of colour vision, loss of visual field, nystagmus, proptosis and strabismus. In patients with NF1-associated OPGs, treatment is initiated when there is evidence of progressive visual loss.[35] Impaired visual field and visual acuity require treatment. Visual acuity is the most important factor in deciding whether to treat NF1-related OPGs or not.[40] Visual acuity is measured using the Snellen chart. The compliance of pediatric patients in visual examinations is challenging. These children may experience difficulties such as young age, developmental delays, attention problems and adaptation issues. In addition, as visual maturation is not complete in children under six years of age, normal visual acuity thresholds vary according to age. Visual field evaluation is very important in OPG; however, computerized and kinetic visual field tests may be difficult to perform in young children due to compliance problems. Thus, ocular coherence tomography can be used as an objective measure of visual acuity in pediatric patients.[41] The unpredictableinimize of OPGs has led to much controversy surrounding follow-up and treatment decisions. Once detected on an MRI scan, they may remain the same size, grow or spontaneously shrink during the follow-up period.[38] Most clinicians accept visual examination as the follow-up criterion, as changes in vision influence decisions regarding follow-up and treatment. However, when visual acuity is unreliable due to problems with children's compliance, MRI results can inform follow-up and treatment. The primary objective of therapy is to minimize the risk of long-term, substantial visual impairment. Decreased visual acuity and radiographic tumor progression are the most common primary indications.[42] In the event of clinical progression, the main treatment option is chemotherapy. Surgery and radiotherapy are not preferred treatment options for NF1-related OPGs, despite being commonly used for other brain tumors. The first-line systemic chemotherapy for patients with OPGs is carboplatin and vincristine.[42] Report of good outcome has been documented concerning the use of first-line cisplatin and etoposide in combination.[43] For patients who do not respond to these drugs, vinblastine or a combination of irinotecan and bevacizumab may be preferred.[42] Radiotherapy is not preferred owing to the risk of developing secondary malignant tumors.[44] It is not possible to perform a total surgery due to the location of the tumor.[35]

Low grade glioma (LGG)

The incidence rate of brainstem gliomas among patients with NF1 is 10%, with most being low-grade tumors.[45] Brainstem gliomas are asymptomatic and rarely obstructive. Close follow-up without treatment is preferred. However, hydrocephalus can develop due to aqueductal stenosis, which can cause headaches and vomiting.[39] The initial treatment approach is conservative. Chemotherapy and surgery are preferred in case of disease progression.[39,46] Most other NF1-related glial tumors are asymptomatic and of low grade, with the most common occurrence site being the temporal lobe, cerebellum, thalamus, basal ganglia, or spinal cord.[46] The treatment choice is dependent on the location and symptoms and includes surgical resection, chemotherapy, and/or conservative approaches.[47]

Targeted therapy for OPG and LGG

Molecular profiling studies have revealed that the pathogenesis of pediatric OPGs and LGGs is driven by aberrations in the Ras-Raf-MEK-ERK (MAPK) pathway, which can serve as a therapeutic target. Selumetinib is reported to exert antitumor effects in pediatric patients with NF1-associated recurrent or refractory LGG. Selumetinib is a potential alternative to chemotherapy in LGG and OPGs.[48,49] Currently, studies are investigating the efficacy and dosage of the MEK inhibitor binimetinib (NCT02285439), as well as the efficacy of the pan-RAF inhibitor tovorafenib (NCT05566795) in NF1-related LGG. For pediatric patients with newly diagnosed *BRAF* V600E mutant LGG, the response to the combination of dabrafenib and trametinib is higher than that to chemotherapy.[50] Additionally, treatment with the mTOR inhibitor everolimus resulted in tumor shrinkage and the stabilization of visual acuity in patients with NF1-associated recurrent or progressive LGG. [51,52] The combination of rapamycin and erlotinib (an EGFR inhibitor) stabilized the disease in some pediatric patients with recurrent LGG.[53]

High Grade Glioma (HGG) and Other Brain Tumors

HGG is rare in children and is usually observed in early adulthood.[54] The most common occurrence sites for HGG are the cerebral hemispheres. The prognosis of HGG is poor. The therapeutic strategies for HGG are surgical resection, radiotherapy, and various chemotherapy agents.[55] An ongoing trial is investigating the efficacy of dabrafenib, trametinib, and hydroxychloroquine in recurrent LGG or HGG with a *BRAF* mutation (NCT04201457). In a series by Rosenfeld et al., five out of 145 patients with NF1 and central nervous system tumors were found to have high-grade tumors, including one case of medulloblastoma and four cases of high-grade glial tumors.[55] Two patients with high-grade gliomas had previously undergone radiotherapy for OPGs. Given the tendency for secondary malignancies to develop, it is important to use radiation therapy in NF1 patients carefully. The correlation between NF1 and medulloblastoma is unclear, although some case reports have been published. Information regarding the medulloblastoma histology of the reported patients is limited, and only one case has a known molecular subgroup.[56] Further studies are needed to elucidate the underlying molecular mechanisms.[56,57] Although most central nervous system tumors in patients with NF1 are low-grade gliomas, clinicians should be highly suspicious of malignancy in patients whose tumors are in an unusual location or behave in an aggressive manner.

Leukemia and Lymphoma

The risk of developing myeloid disorders, particularly juvenile myelomonocytic leukemia (JMML), is increased by up to 500-fold in children with NF1. NF1 is correlated with JMML, and 15% of JMML cases are associated with NF1.[58] Patients with JMML, a rapidly progressing condition, typically present with symptoms, such as hepatomegaly, fever, pallor, rash, and lymphadenopathy.[59] T lymphoblastic

lymphoma is the most common lymphoma in patients with NF1 and is associated with low survival rates.[60] Case reports have described an association between NF1 and Hodgkin's lymphoma, although this is considered coincidental.[57] The potential therapeutic effect of MEK inhibitors on JMML can be attributed to the activation of RAS signaling. An ongoing study is evaluating the efficacy of the MEK inhibitor trametinib in patients with relapsed or refractory JMML (NCT03190915).

Rhabdomyosarcoma (RMS)

RMS is the most common type of soft tissue cancer in children, accounting for around 40–50% of cases.[61] The incidence of RMS in patients with NF1 is higher than that in the general population. Compared to sporadic RMS, tumors are almost exclusively the embryonal subtype.[62] The most common site for RMS occurrence is the urogenital system.[62] The age of RMS occurrence in patients with NF1 is lower than that in patients with sporadic NF1.[62,63] There is no data to suggest that the outcomes of RMS in the NF1 population differ from those of the general population. The treatment options and survival rates are similar for patients with and without NF1.[64] In a series by Crucis et al. they reported 16 RMS cases with NF1.[62] The long-term sequelae related to chemotherapy are not obviously different from those of non-NF1 patients. The 5-year event-free survival and overall survival were 67% and 87%, respectively.

Malignant Melanoma

Although the development of malignant melanoma in patients with NF1 has been documented in various clinical reports, very little is known about the characteristics of melanomas that occur in this patient group.[65] Some case reports have suggested a correlation between malignant melanoma and NF1. However, large population studies have not provided clear evidence.[66] Due to these scarce results, surveillance for malignant melanoma has typically not been recommended.[67,68] The MEK inhibitors cobimetinib and trametinib have been used to treat malignant melanoma in adult patients with NF1.[69,70]

Other Tumors

The incidence rates of breast cancer, gastrointestinal stromal tumors, carcinoid tumors, and pheochromocytoma in adult patients with NF1 are higher than those in pediatric patients with NF1.[71-73] The prognosis and treatment are similar to those of patients without NF1, except for breast cancer.[74] The increased breast cancer risk among younger women with NF1 means they should be offered more screening than females in the general population. Annual mammography should be recommended in patients with NF1 in national high-risk screening programs. The National Comprehensive Cancer Network recommends annual mammography beginning at age 30, as well as consideration of breast MRI between ages 30 and 50.[75] The aggressiveness of breast cancer with NF1 is higher than that of sporadic breast cancer. Patients with NF1-associated breast cancer exhibit poor prognostic features, such as a high frequency of high-grade tumors, hormone receptor negativity, and HER2 overexpression.[76] The incidence of pheochromocytoma associated with NF1 has been reported as ranging from 0.1% to 5.7%. They cause hypertension in most individuals who experience symptoms. Histopathology is more often benign than malignant.[77]

Conclusion

NF1 is an autosomal dominant neurocutaneous disease that significantly increases the risk of developing cancer. Patients with NF1 are also predisposed to developing benign tumors. Although there is no cure for NF1, identifying patients with NF1 and conducting intermittent follow-ups are important for early detection of potential complications, particularly tumorigenesis. The treatment options for NF1-

related cancers, which include chemotherapy, radiotherapy, and surgery, are planned according to the type of cancer.

PNs are usually benign, but as they grow, they can cause serious health problems, including pain and damage to the surrounding tissues. Treatment may be necessary due to their location and the resulting morbidity and functional impairment. Most patients are not eligible for surgery as the tumor is located deeply along the nerve tract. The discovery of the molecular pathogenesis and the biological basis of this disorder has enabled the development of targeted therapies.

Treatment is required for patients with OPG, another type of benign tumor, if there is impairment to their visual field or acuity. In the event of clinical progression, the main treatment option is chemotherapy. Surgery and radiotherapy are not preferred treatment options for NF1-related OPGs, despite being commonly used for other brain tumors. Targeted therapy is a potential alternative to chemotherapy in OPGs.

New insights into the pathogenesis of the disease now offer hope for the development of specific, less toxic, and more precise molecularly targeted treatment methods.

Author contribution

The author confirm contribution to the paper as follows: Review conception and design: HSŞ; literature review: HSŞ; draft manuscript preparation: HSŞ. The author reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Legius E, Messiaen L, Wolkenstein P, et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med 2021; 23: 1506-1513. https://doi.org/10.1038/s41436-021-01170-5
2. Biotteau M, Déjean S, Lelong S, et al. Sporadic and familial variants in NF1: an explanation of the wide variability in neurocognitive phenotype? Front Neurol 2020; 11: 368. https://doi.org/10.3389/fneur.2020.00368
3. Peduto C, Zanobio M, Nigro V, Perrotta S, Piluso G, Santoro C. Neurofibromatosis type 1: pediatric aspects and review of genotype-phenotype correlations. Cancers (Basel) 2023; 15: 1217. https://doi.org/10.3390/cancers15041217
4. Ponti G, Tomasi A, Pastorino L, et al. Diagnostic and pathogenetic role of café-au-lait macules in nevoid basal cell carcinoma syndrome. Hered Cancer Clin Pract 2012; 10: 15. https://doi.org/10.1186/1897-4287-10-15
5. Fisher MJ, Blakeley JO, Weiss BD, et al. Management of neurofibromatosis type 1-associated plexiform neurofibromas. Neuro Oncol 2022; 24: 1827-1844. https://doi.org/10.1093/neuonc/noac146
6. Ferner RE, Thomas M, Mercer G, et al. Evaluation of quality of life in adults with neurofibromatosis 1 (NF1) using the Impact of NF1 on Quality of Life (INF1-QOL) questionnaire. Health Qual Life Outcomes 2017; 15: 34. https://doi.org/10.1186/s12955-017-0607-y

7. Needle MN, Cnaan A, Dattilo J, et al. Prognostic signs in the surgical management of plexiform neurofibroma: the Children's Hospital of Philadelphia experience, 1974-1994. J Pediatr 1997; 131: 678-682. https://doi.org/10.1016/s0022-3476(97)70092-1

8. Robertson KA, Nalepa G, Yang FC, et al. Imatinib mesylate for plexiform neurofibromas in patients with neurofibromatosis type 1: a phase 2 trial. Lancet Oncol 2012; 13: 1218-1224. https://doi.org/10.1016/S1470-2045(12)70414-X

9. Weiss B, Widemann BC, Wolters P, et al. Sirolimus for non-progressive NF1-associated plexiform neurofibromas: an NF clinical trials consortium phase II study. Pediatr Blood Cancer 2014; 61: 982-986. https://doi.org/10.1002/pbc.24873

10. Widemann BC, Babovic-Vuksanovic D, Dombi E, et al. Phase II trial of pirfenidone in children and young adults with neurofibromatosis type 1 and progressive plexiform neurofibromas. Pediatr Blood Cancer 2014; 61: 1598-1602. https://doi.org/10.1002/pbc.25041

11. Widemann BC, Dombi E, Gillespie A, et al. Phase 2 randomized, flexible crossover, double-blinded, placebo-controlled trial of the farnesyltransferase inhibitor tipifarnib in children and young adults with neurofibromatosis type 1 and progressive plexiform neurofibromas. Neuro Oncol 2014; 16: 707-718. https://doi.org/10.1093/neuonc/nou004

12. Jakacki RI, Dombi E, Steinberg SM, et al. Phase II trial of pegylated interferon alfa-2b in young patients with neurofibromatosis type 1 and unresectable plexiform neurofibromas. Neuro Oncol 2017; 19: 289-297. https://doi.org/10.1093/neuonc/now158

13. McCowage GB, Mueller S, Pratilas CA, et al. Trametinib in pediatric patients with neurofibromatosis type 1 (NF-1)-associated plexiform neurofibroma: a phase I/IIa study. J Clin Oncol 2018; 36(Suppl. 15): 10504. https://doi.org/10.1200/JCO.2018.36.15_suppl.10504

14. Fisher M. NF105: a Neurofibromatosis Clinical Trials Consortium (NFCTC) phase II study of cabozantinib (XL184) for neurofibromatosis type 1 (NF1) associated plexiform neurofibromas. Paper presented at: 2018 Joint Global Neurofibromatosis Conference, 2018.

15. Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. N Engl J Med 2020; 382: 1430-1442. https://doi.org/10.1056/NEJMoa1912735

16. Armstrong AE, Belzberg AJ, Crawford JR, Hirbe AC, Wang ZJ. Treatment decisions and the use of MEK inhibitors for children with neurofibromatosis type 1-related plexiform neurofibromas. BMC Cancer 2023; 23: 553. https://doi.org/10.1186/s12885-023-10996-y

17. Moertel CL, Hirbe AC, Shuhaiber HH, et al. 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: 716-729. https://doi.org/10.1200/JCO.24.01034

18. Evans DGR, Baser ME, McGaughran J, Sharif S, Howard E, Moran A. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet 2002; 39: 311-314. https://doi.org/10.1136/jmg.39.5.311

19. Spunt SL, Million L, Chi YY, et al. A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. Lancet Oncol 2020; 21: 145-161. https://doi.org/10.1016/S1470-2045(19)30672-2

20. Ferrari A, Orbach D, Sparber-Sauer M, et al. The treatment approach to pediatric non-rhabdomyosarcoma soft tissue sarcomas: a critical review from the INternational Soft Tissue SaRcoma ConsorTium. Eur J Cancer 2022; 169: 10-19. https://doi.org/10.1016/j.ejca.2022.03.028

21. Friedrich RE, Hartmann M, Mautner VF. Malignant peripheral nerve sheath tumors (MPNST) in NF1-affected children. Anticancer Res 2007; 27: 1957-1960.

22. Lozouet M, Paul L, Kallel M, Braux G, Leclerc A, Emery E. Trigeminal malignant peripheral nerve-sheath tumor: systematic review, and case report treated by proton-beam therapy. Neurochirurgie 2025; 71: 101621. https://doi.org/10.1016/j.neuchi.2024.101621

23. Bachmann N, Leiser D, Pica A, Bachtiary B, Weber DC. Clinical outcome after pencil beam scanning proton therapy of patients with non-metastatic malignant and benign peripheral nerve sheath tumors. Front Oncol 2022; 12: 881665. https://doi.org/10.3389/fonc.2022.881665

24. Ferrari A, Bergamaschi L, Chiaravalli S, et al. Malignant peripheral nerve sheath tumor in children and adolescents: local treatment in a retrospective single-center experience. Pediatr Blood Cancer 2025; 72: e31813. https://doi.org/10.1002/pbc.31813

25. Martin E, Flucke UE, Coert JH, van Noesel MM. Treatment of malignant peripheral nerve sheath tumors in pediatric NF1 disease. Childs Nerv Syst 2020; 36: 2453-2462. https://doi.org/10.1007/s00381-020-04687-3

26. Kim AR BK, Wolters P, et al. SARC031: a phase 2 trial of selumetinib and sirolimus for patients with unresectable or metastatic malignant peripheral nerve sheath tumors. Vancouver, Canada: Connective Tissue Oncology Society; November 17, 2022.

27. Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet 2016; 388: 488-497. https://doi.org/10.1016/S0140-6736(16)30587-6

28. Ferguson MJ, Rhodes SD, Jiang L, et al. Preclinical evidence for the use of sunitinib malate in the treatment of plexiform neurofibromas. Pediatr Blood Cancer 2016; 63: 206-213. https://doi.org/10.1002/pbc.25763

29. Kim A, Dombi E, Tepas K, et al. Phase I trial and pharmacokinetic study of sorafenib in children with neurofibromatosis type I and plexiform neurofibromas. Pediatr Blood Cancer 2013; 60: 396-401. https://doi.org/10.1002/pbc.24281

30. Ahsan S, Ge Y, Tainsky MA. Combinatorial therapeutic targeting of BMP2 and MEK-ERK pathways in NF1-associated malignant peripheral nerve sheath tumors. Oncotarget 2016; 7: 57171-57185. https://doi.org/10.18632/oncotarget.11036

31. Albritton K, Rankin C, Coffin C, et al. Phase II study of erlotinib in metastatic or unresectable malignant peripheral nerve sheath tumors (MPNST). J Clin Oncol 2006; 24(Suppl. 18): 9518. https://doi.org/10.1200/jco.2006.24.18_suppl.9518

32. Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. J Clin Oncol 2009; 27: 3133-3140. https://doi.org/10.1200/JCO.2008.20.4495

33. Schuetze SM, Wathen JK, Lucas DR, et al. SARC009: Phase 2 study of dasatinib in patients with previously treated, high-grade, advanced sarcoma. Cancer 2016; 122: 868-874. https://doi.org/10.1002/cncr.29858

34. Widemann BC, Meyer CF, Cote GM, et al. SARC016: Phase II study of everolimus in combination with bevacizumab in sporadic and neurofibromatosis type 1 (NF1) related refractory malignant peripheral nerve sheath tumors (MPNST). J Clin Oncol 2016; 34(Suppl. 15): 11053. https://doi.org/10.1200/JCO.2016.34.15_suppl.11053

35. Listernick R, Ferner RE, Liu GT, Gutmann DH. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. Ann Neurol 2007; 61: 189-198. https://doi.org/10.1002/ana.21107

36. de Blank PM, Fisher MJ, Liu GT, et al. Optic pathway gliomas in neurofibromatosis type 1: an update: surveillance, treatment indications, and biomarkers of vision. J Neuroophthalmol 2017; 37(Suppl 1): S23-S32. https://doi.org/10.1097/WNO.0000000000000550

37. Blanchard G, Lafforgue MP, Lion-François L, et al. Systematic MRI in NF1 children under six years of age for the diagnosis of optic pathway gliomas. Study and outcome of a French cohort. Eur J Paediatr Neurol 2016; 20: 275-281. https://doi.org/10.1016/j.ejpn.2015.12.002

38. Taylor T, Jaspan T, Milano G, et al. Radiological classification of optic pathway gliomas: experience of a modified functional classification system. Br J Radiol 2008; 81: 761-766. https://doi.org/10.1259/bjr/65246351

39. Glombova M, Petrak B, Lisy J, Zamecnik J, Sumerauer D, Liby P. Brain gliomas, hydrocephalus and idiopathic aqueduct stenosis in children with neurofibromatosis type 1. Brain Dev 2019; 41: 678-690. https://doi.org/10.1016/j.braindev.2019.04.003

40. Avery RA, Bouffet E, Packer RJ, Reginald A. Feasibility and comparison of visual acuity testing methods in children with neurofibromatosis type 1 and/or optic pathway gliomas. Invest Ophthalmol Vis Sci 2013; 54: 1034-1038. https://doi.org/10.1167/iovs.12-11385

41. Banc A, Stan C, Florian IS. Optical coherence tomography as a marker of vision in children with optic pathway gliomas. Childs Nerv Syst 2018; 34: 51-60. https://doi.org/10.1007/s00381-017-3578-8

42. Fisher MJ, Loguidice M, Gutmann DH, et al. Visual outcomes in children with neurofibromatosis type 1-associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. Neuro Oncol 2012; 14: 790-797. https://doi.org/10.1093/neuonc/nos076

43. Varan A, Batu A, Cila A, et al. Optic glioma in children: a retrospective analysis of 101 cases. Am J Clin Oncol 2013; 36: 287-292. https://doi.org/10.1097/COC.0b013e3182467efa

44. Sharif S, Upadhyaya M, Ferner R, et al. A molecular analysis of individuals with neurofibromatosis type 1 (NF1) and optic pathway gliomas (OPGs), and an assessment of genotype-phenotype correlations. J Med Genet 2011; 48: 256-260. https://doi.org/10.1136/jmg.2010.081760

45. Mahdi J, Shah AC, Sato A, et al. A multi-institutional study of brainstem gliomas in children with neurofibromatosis type 1. Neurology 2017; 88: 1584-1589. https://doi.org/10.1212/WNL.0000000000003881

46. Guillamo JS, Créange A, Kalifa C, et al. Prognostic factors of CNS tumours in Neurofibromatosis 1 (NF1): a retrospective study of 104 patients. Brain 2003; 126: 152-160. https://doi.org/10.1093/brain/awg016

47. Byrne S, Connor S, Lascelles K, Siddiqui A, Hargrave D, Ferner RE. Clinical presentation and prognostic indicators in 100 adults and children with neurofibromatosis 1 associated non-optic pathway brain gliomas. J Neurooncol 2017; 133: 609-614. https://doi.org/10.1007/s11060-017-2475-z

48. Fangusaro J, Onar-Thomas A, Young Poussaint T, et al. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial. Lancet Oncol 2019; 20: 1011-1022. https://doi.org/10.1016/S1470-2045(19)30277-3

49. Banerjee A, Jakacki RI, Onar-Thomas A, et al. A phase I trial of the MEK inhibitor selumetinib (AZD6244) in pediatric patients with recurrent or refractory low-grade glioma: a Pediatric Brain Tumor Consortium (PBTC) study. Neuro Oncol 2017; 19: 1135-1144. https://doi.org/10.1093/neuonc/now282

50. Bouffet E, Hansford JR, Garrè ML, et al. Dabrafenib plus trametinib in pediatric glioma with BRAF V600 Mutations. N Engl J Med 2023; 389: 1108-1120. https://doi.org/10.1056/NEJMoa2303815

51. Ullrich NJ, Prabhu SP, Packer RJ, et al. Visual outcomes following everolimus targeted therapy for neurofibromatosis type 1-associated optic pathway gliomas in children. Pediatr Blood Cancer 2021; 68: e28833. https://doi.org/10.1002/pbc.28833

52. Ullrich NJ, Prabhu SP, Reddy AT, et al. A phase II study of continuous oral mTOR inhibitor everolimus for recurrent, radiographic-progressive neurofibromatosis type 1-associated pediatric low-grade glioma: a Neurofibromatosis Clinical Trials Consortium study. Neuro Oncol 2020; 22: 1527-1535. https://doi.org/10.1093/neuonc/noaa071

53. Yalon M, Rood B, MacDonald TJ, et al. A feasibility and efficacy study of rapamycin and erlotinib for recurrent pediatric low-grade glioma (LGG). Pediatr Blood Cancer 2013; 60: 71-76. https://doi.org/10.1002/pbc.24142

54. D'Angelo F, Ceccarelli M, Tala , et al. The molecular landscape of glioma in patients with Neurofibromatosis 1. Nat Med 2019; 25: 176-187. https://doi.org/10.1038/s41591-018-0263-8

55. Rosenfeld A, Listernick R, Charrow J, Goldman S. Neurofibromatosis type 1 and high-grade tumors of the central nervous system. Childs Nerv Syst 2010; 26: 663-667. https://doi.org/10.1007/s00381-009-1024-2

56. Ranalli M, Boni A, Caroleo AM, et al. Molecular characterization of medulloblastoma in a patient with neurofibromatosis type 1: case report and literature review. Diagnostics (Basel) 2021; 11: 647. https://doi.org/10.3390/diagnostics11040647

57. Varan A, Şen H, Aydın B, Yalçın B, Kutluk T, Akyüz C. Neurofibromatosis type 1 and malignancy in childhood. Clin Genet 2016; 89: 341-345. https://doi.org/10.1111/cge.12625

58. Side L, Taylor B, Cayouette M, et al. Homozygous inactivation of the NF1 gene in bone marrow cells from children with neurofibromatosis type 1 and malignant myeloid disorders. N Engl J Med 1997; 336: 1713-1720. https://doi.org/10.1056/NEJM199706123362404

59. Aricò M, Biondi A, Pui CH. Juvenile myelomonocytic leukemia. Blood 1997; 90: 479-488.

60. Bergqvist C, Hemery F, Jannic A, Ferkal S, Wolkenstein P. Lymphoproliferative malignancies in patients with neurofibromatosis 1. Orphanet J Rare Dis 2021; 16: 230. https://doi.org/10.1186/s13023-021-01856-8

61. Ognjanovic S, Linabery AM, Charbonneau B, Ross JA. Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975-2005. Cancer 2009; 115: 4218-4226. https://doi.org/10.1002/cncr.24465

62. Crucis A, Richer W, Brugières L, et al. Rhabdomyosarcomas in children with neurofibromatosis type I: a national historical cohort. Pediatr Blood Cancer 2015; 62: 1733-1738. https://doi.org/10.1002/pbc.25556

63. Patil S, Chamberlain RS. Neoplasms associated with germline and somatic NF1 gene mutations. Oncologist 2012; 17: 101-116. https://doi.org/10.1634/theoncologist.2010-0181

64. Sung L, Anderson JR, Arndt C, Raney RB, Meyer WH, Pappo AS. Neurofibromatosis in children with Rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma study IV. J Pediatr 2004; 144: 666-668. https://doi.org/10.1016/j.jpeds.2004.02.026

65. Guillot B, Dalac S, Delaunay M, et al. Cutaneous malignant melanoma and neurofibromatosis type 1. Melanoma Res 2004; 14: 159-163. https://doi.org/10.1097/00008390-200404000-00014

66. Uusitalo E, Rantanen M, Kallionpää RA, et al. Distinctive cancer associations in patients with neurofibromatosis type 1. J Clin Oncol 2016; 34: 1978-1986. https://doi.org/10.1200/JCO.2015.65.3576

67. Perrino MR, Das A, Scollon SR, et al. Update on pediatric cancer surveillance recommendations for patients with neurofibromatosis type 1, noonan syndrome, CBL syndrome, costello syndrome, and related RASopathies. Clin Cancer Res 2024; 30: 4834-4843. https://doi.org/10.1158/1078-0432.CCR-24-1611

68. Zhang M, Bhat T, Gutmann DH, Johnson KJ. Melanoma in individuals with neurofibromatosis type 1: a retrospective study. Dermatol Online J 2019; 25: 13030/qt5ck3f722. https://doi.org/10.5070/D32511046137

69. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016; 17: 1248-1260. https://doi.org/10.1016/S1470-2045(16)30122-X

70. Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III braf-mutated melanoma. N Engl J Med 2017; 377: 1813-1823. https://doi.org/10.1056/NEJMoa1708539

71. Miettinen M, Fetsch JF, Sobin LH, Lasota J. Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol 2006; 30: 90-96. https://doi.org/10.1097/01.pas.0000176433.81079.bd

72. Salvi PF, Lorenzon L, Caterino S, Antolino L, Antonelli MS, Balducci G. Gastrointestinal stromal tumors associated with neurofibromatosis 1: a single centre experience and systematic review of the literature including 252 cases. Int J Surg Oncol 2013; 2013: 398570. https://doi.org/10.1155/2013/398570

73. Kalkan E, Waguespack SG. Endocrine tumors associated with neurofibromatosis type 1, Peutz-Jeghers syndrome and other familial neoplasia syndromes. Front Horm Res 2013; 41: 166-181. https://doi.org/10.1159/000345676

74. Evans DGR, Kallionpää RA, Clementi M, et al. Breast cancer in neurofibromatosis 1: survival and risk of contralateral breast cancer in a five country cohort study. Genet Med 2020; 22: 398-406. https://doi.org/10.1038/s41436-019-0651-6

75. Gradishar WJ, Anderson BO, Abraham J, et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2020; 18: 452-478. https://doi.org/10.6004/jnccn.2020.0016

76. Seminog OO, Goldacre MJ. Age-specific risk of breast cancer in women with neurofibromatosis type 1. Br J Cancer 2015; 112: 1546-1548. https://doi.org/10.1038/bjc.2015.78

77. Walther MM, Herring J, Enquist E, Keiser HR, Linehan WM. von Recklinghausen's disease and pheochromocytomas. J Urol 1999; 162: 1582-1586.