NF1 e neurofibromi plessiformi: approcci innovativi per una gestione multidisciplinare

Teresa Perillo, MD

Unità Operativa Complessa di Pediatria ad Indirizzo Oncoematologico

Azienda Ospedaliera Universitaria Policlinico Consorziale di Bari

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Ipsen						x	
Merck						x	
Alexion						x	

NF1 affects approximately 1 in 2,500 births and can reduce life expectancy by approximately 15 years

Global Incidence

1 in 2500 births[1,2]

50% spontaneous

variant with no family history of NF1[3]

50% inherited

as an autosomal-dominant variant in the *NF1* gene[4]

100% penetrance

by age 20 with highly variable expression[4]



Occurs equally worldwide

in both sexes and all ethnicities*[,3,5,8]

Global Prevalence

1 in 3200 individuals[1,5]

Life expectancy

reduced by ~**15 years**[6]

Approximately

230,000 individuals in Europe

are estimated to have NF1*[,†,5,8-10]

NF1, neurofibromatosis type 1

*This claim is substantiated by estimates generated from a study among German paediatric patients at elementary school enrolment and a population-based study in Southeast Wales; it may not be representative of all patient populations.[5,8] †This claim is substantiated by a study conducted in a United Kingdom genetic registry in the Manchester region of Northwest England; it may not be representative of all patient populations.[9]

1. Lee TJ, et al. *Orphanet J Rare Dis.* 2023;18(1):292. 2. Children's Tumor Foundation. New and improved: The way to talk about NF. Press release. May 9, 2023. Accessed July 21, 2025. https://www.ctf.org/news/new-and-improved-the-way-to-talk-about-nf/ 3. Hirbe AC, et al. *Lancet Neurol*. 2014;13(8):834-843. 4. Boyd KP, et al. *J Am Acad Dermatol*. 2009;61(1):1-16. 5. Lammert M, et al. *Arch Dermatol*. 2005;141(1):71-74. 6. Evans DG, et al. *Eur J Hum Genet*. 2011;19(11):1187-1191. 7. Kallionpää RA, et al. *Genet Med*. 2018;20(9):1082-1086. 8. Huson SM, et al. *Brain*. 1988;111(6):1355-1381. 9. Evans DG, et al. *Am J Hum Genet*. 2010;152A:327–332. 10. Lee TJ, et al. *Orphanet J Rare Dis.* 2023;18(1):292

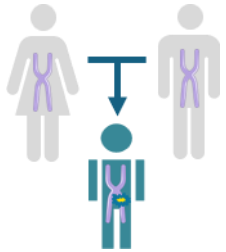
NF1 can arise through inherited or de novo variants of the NF1 gene

- *NF1* is inherited in an autosomal dominant pattern[1,2,3]
- A single mutated copy of the *NF1* gene is sufficient to cause the disorder[1,2,3]
- An individual with NF1 has a 50% chance of transmitting the pathogenic *NF1* gene variant to each child, regardless of sex[1,2,3]

The Genetic transmission of *NF1* gene variants[3,4]

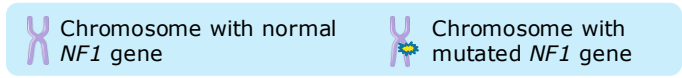
1 *De novo* mutation

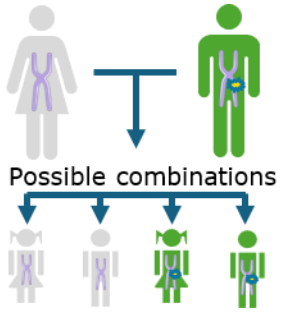
For ~**50%** of patients, NF1 arises from a **spontaneous (*de novo*) mutation in the *NF1* gene**



2 Inherited transmission

~50% of patients inherit a germline *NF1* gene variant from one parent





Both routes give an ***NF1* +/−** genotype in all cells (one mutated, one normal allele), reducing neurofibromin production (**haploinsufficiency**) as a background for the NF1 phenotype

Bi-allelic *NF1* inactivation[5]

- Patients with NF1 are predisposed to developing malignancies, including MPNSTs and leukemias
- Tumors arise after a **somatic "second-hit" mutation** in the remaining *NF1* allele, causing loss of heterozygosity (*NF1*−/−) and complete loss of neurofibromin

Mosaic *NF1* Genetic Variants[6]

- There are pathogenic *NF1* gene variants beyond the classic generalized form, including mosaic neurofibromatosis
- Mosaic neurofibromatosis results from mutation of the ***NF1* gene in early embryogenesis** rather than at conception
- **Clinical features**, for example CALMs and freckling, are **confined to one side or area of the body**

1. Yap YS et al., *Oncotarget*. 2014;5(15):5873-5892; 2. Gutmann DH et al., *Nat Rev Dis Primers*. 2017;3:170004; 3. Miller DT et al., *Pediatrics*. 2019;143(5):e20190660; 4. Adam MP, et al, eds. GeneReviews®. University of Washington, Seattle; 1993-2024. Updated April 3, 2025; 5. Doris Steinemann et al., Haematologica 2010; 95(2):320-323; 6. Boyd KP et al., *J Am Acad Dermatol*. 2009;61(1):1-16

Specific NF1 gene variants can influence disease severity, correlating with specific phenotypes



A selection of known genotype-phenotype correlations as of 2023[1]

	Gene variant	Linked phenotype
Severe disease	17q11.2 microdeletion[1]	• Intellectual disability, increased neurofibroma count, cardiovascular risks, and a higher likelihood of malignancies such as MPNST • Often includes plexiform neurofibromas (PNs) and optic pathway gliomas (OPGs)
	Missense variant affecting codons from 844-848	• Greater incidence of plexiform and symptomatic spinal neurofibromas, optic pathway gliomas, and skeletal abnormalities
Mild disease	c.5425C>T missense mutation resulting in p.Arg1809Cys[2,3,4]	• Learning disabilities; absence of cutaneous or PNs; presence of pulmonic stenosis
	Deletion c.2970-2972delAAT in exon 17	• Milder phenotype with absence of cutaneous or plexiform neurofibromas; low-grade non-OPGs, cognitive disabilities
	Methionine 1149 Variant	• Asymptomatic or mild conditions and typically lacks PNs or OPGs

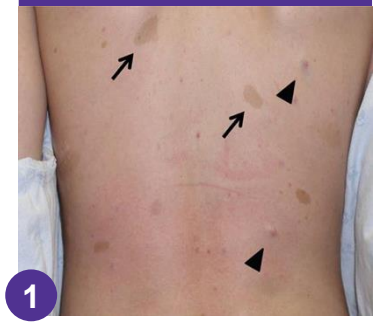
1. Yap YS et al., *Oncotarget*. 2014;5(15):5873-5892; 2.Miller DT et al., Pediatrics. 2019;143(5):e20190660; 3.Koczkowska M et al., *Am J Hum Genet*. 2018;102:69-87; 4. Pinna V et al., *Eur J Hum Genet*. 2015;23(8):1068-1071

Diagnostic Criteria for NF1

One or more of 7 clinical criteria are required for a diagnosis of an individual with a parent who meets the diagnostic criteria[1–6]

Diagnosis Requires Presence of ≥2 of the Following 7 Clinical Criteria in an Individual who Does Not Have a Parent Diagnosed with NF1[1]

Café Au Lait Macules*,[2]



1

≥6 CALMs† (arrows: CALMs, arrowheads: cNF)[1,2]

Cutaneous Neurofibroma*,[2]



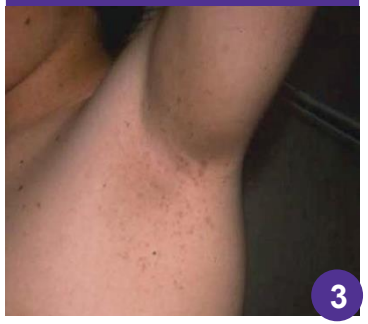
2

Plexiform Neurofibroma*,[2]



≥2 neurofibromas of any type or 1 PN

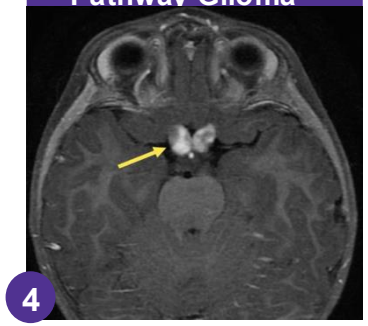
Skinfold Freckling*,[2]



3

Freckling in the axillary or inguinal regions†

Optic Pathway Glioma*,[2]



4

Optic pathway glioma

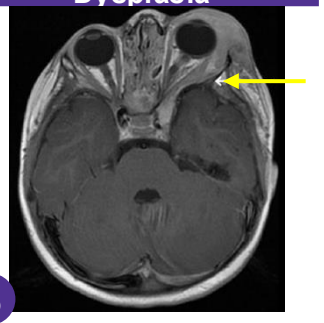
Lisch Nodules[7]



5

≥2 iris Lisch nodules or ≥2 choroidal abnormalities[1]

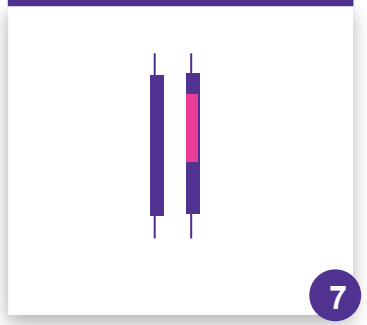
Sphenoid Wing Dysplasia[8]



6

Magnetic resonance imaging (MRI) of infiltrative orbital periorbital plexiform neurofibroma (OPPN) and sphenoid wing dysplasia

NF1 Variant[1]



7

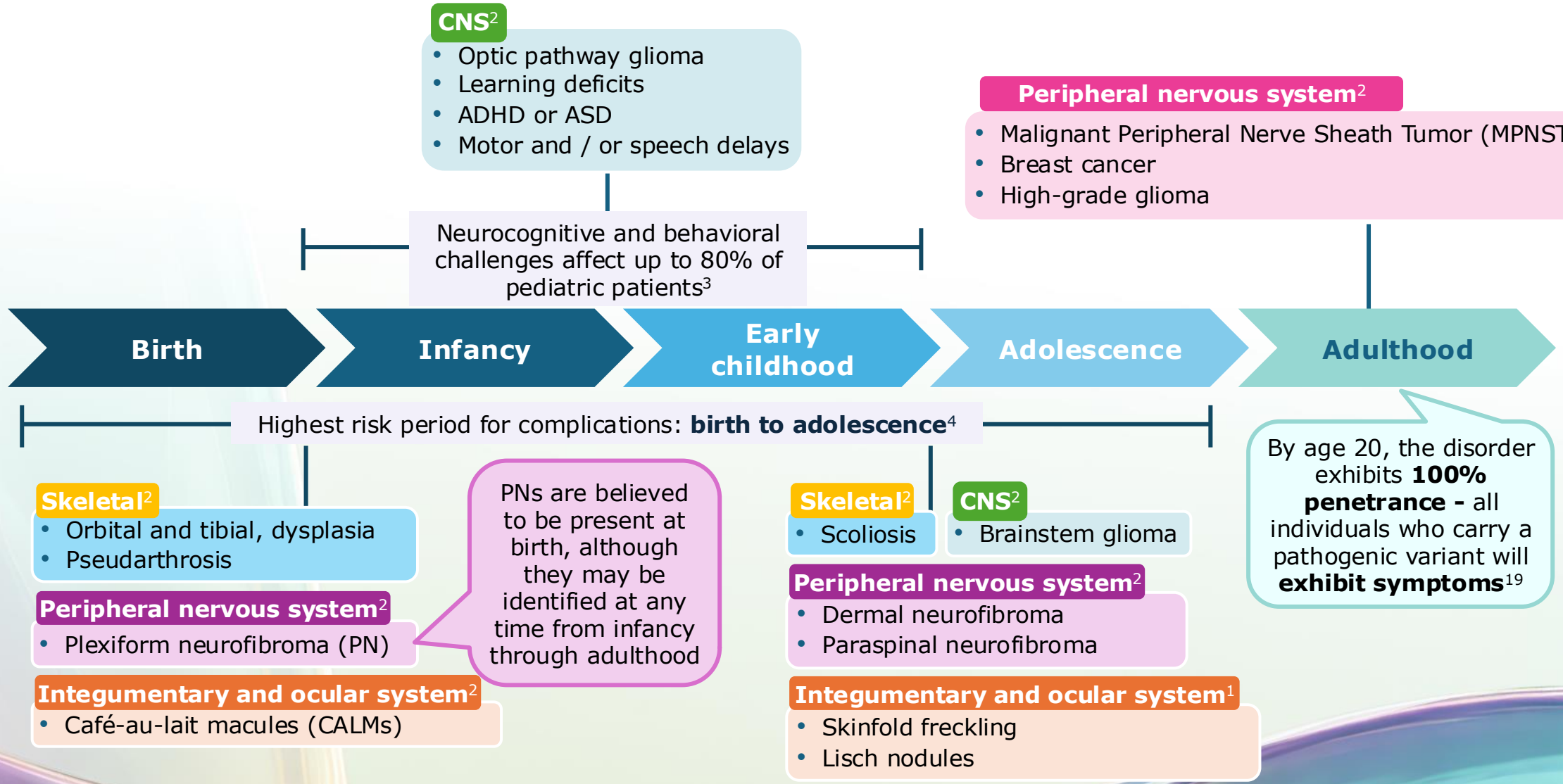
Heterozygous pathogenic variant

CALM, café au lait macules; cNF, cutaneous neurofibroma; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; OPPN, orbital periorbital plexiform neurofibroma; PN, plexiform neurofibroma.

*Figures are reproduced with permission from American Academy of Pediatrics (Miller DT, et al. 2019).[2] †If only CALM and freckling are present, ≥1 of the 2 pigmentary findings (CALM or freckling) should be bilateral.[1]

1. Legius E, et al. *Genet Med*. 2021;23:1506-1513. 2. Miller DT, et al. *Pediatrics*. 2019;143(5):e20190660. 3. Bergqvist C, et al. *Orphanet J Rare Dis*. 2020;15(37). 4. Ferner RE, et al. *J Med Genet*. 2007;44(2):81–88. 5. Farschtschi S, et al. *Dtsch Arztebl Int*. 2025;122:71–6. 6. Sunder-Plassmann V, et al. *Wien Klin Wochenschr*. 2024. 7. Adams EG, et al. *Case Rep Ophthalmol Med*. 2011;2011:854784. 8. Avery RA, et al. *Ophthalmology*. 2017;124(1):123-132.

NF1 manifestations evolve throughout life, with the risk of serious complications increasing with age



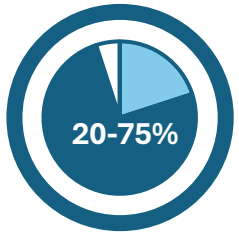
1.Laycock-van Spyk S, Thomas N, Cooper DN, et al., *Hum Genomics*. 2011;5(6):623-690; 2. Gutmann DH, Ferner RE, Listernick RH, et al., *Nat Rev Dis Primers*. 2017;3:17004; 3.Torres Nupan MM, Velez Van Meerbeke A, López Cabra CA, et al., *Front Pediatr*. 2017;5:227; 4. Jett K, Friedman JM. Clinical and genetic aspects of neurofibromatosis 1. *Genet Med*. 2010;12(1):1-11; 5.Boyd KP, Korf BR, Theos A. Neurofibromatosis type 1. *J Am Acad Dermatol*. 2009;61(1):1-16.

Cognitive, behavioral, and neurologic manifestations of NF1 can impact academic and social functioning

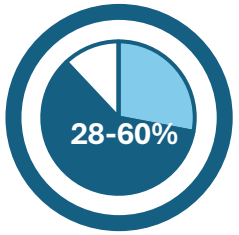
Cognitive, learning, attention, executive function, and autism spectrum disorder (ASD) deficits are more common in NF1

Sleep issues, headaches, seizures, and psychiatric complications may require neuroimaging assessments[6-9, 10]

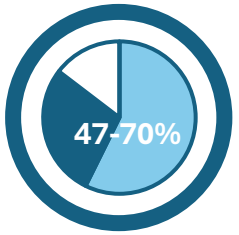
Neurocognitive deficits



Academic learning difficulties[1]

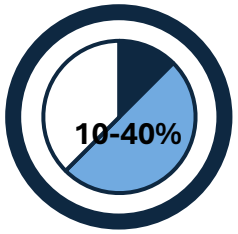


ADHD[2,3]



Academic underperformance vs ability[4,5]

Behavioral deficits



Diagnosed with ASD[2,5]

Deficits shifted toward the more symptomatic end of the spectrum[4]



Score within impaired range[1]

>50% of pediatrics experience sleep disturbances*[6,7]



- Prolonged sleep onset latency (difficulty falling asleep)
- More awakenings during the night
- Reduced sleep duration

78% of patients experience reported headaches†[8]



- 83% meet the International Headache Society diagnostic criteria for migraines (with or without aura)
- 11% reporting chronic daily headache

4-10% of patients experience Seizures‡[4]



- Mainly due to intracranial tumors

*This estimate was generated from a single-center retrospective study (location unknown) and a cross-sectional study in registered patients in the Oxford Clinical Genetics Neurofibromatosis Database (UK; N=41). †Headache was reported by 90 of 115 patients with NF1 in a cross-sectional survey at the London NF clinic. ‡ This estimate was generated from a retrospective study in patients with NF1 attending the Pediatric Tertiary Center of NF in Naples, Italy (N=437)

1. Vogel AC, Gutmann DH, Morris SM., Dev Med Child Neurol. 2017;59(11):1112-1116; 2.Rietman A. Genotype and behavioral phenotype in children with neurofibromatosis type 1. Presented at: 2018 Joint Global Neurofibromatosis Conference; November 2-6, 2018; Paris, France; 3. Roy A, et al., Orphanet J Rare Dis. 2021;16(420); 4. Lehtonen A, Howie E, Trump D, Huson SM., Dev Med Child Neurol. 2013;55(2):111-125; 5. Geoffray M-M, et al., J Psychiatr Res. 2021;140:545–550; 6.Licis AK, Vallorani A, Gao F, et al. J Child Neurol. 2013;28(11):1400-1405; 7. Johnson H, et al. Dev Med Child Neurol. 2005;47:237–242; 8. Afridi SK, Leschziner GD, Ferner RE., Am J Med Genet A. 2015;167A(10):2282-2285; 9. Santoro C, Bernardo P, Coppola A, et al., Ital J Pediatr. 2018;44(1):41.; 10. Miller DT, Freedenberg D, Schorry E, et al., Pediatrics. 2019;143(5):e20190660.

Optic Pathway Gliomas (OPGs) are common in children but have variable visual outcomes

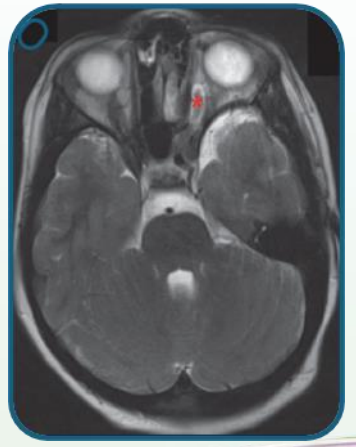
Optic Pathway Glioma (OPG)

- Patients with NF1 are prone to developing CNS tumors known as **gliomas** which affect the **optic nerves**[2]
- Gliomas are **most common in children <7 years old** (mean 4.5 years)[2]
- Around **15–20% of children develop optic pathway tumors**[2,3] and among those, **30–50% experience vision loss**[4-6]
- Girls are 5-10x more likely to need treatment and experience visual decline[2]

Clinical manifestations of OPG are related to location[1]

OPGs are a type of pilocytic astrocytoma and represent the most common brain tumors in pediatric patients with NF1. These tumors typically exhibit low mitotic activity and low proliferative indices but can lead to irreversible vision loss or blindness in some patients[6]

Optic nerve	• Thickening of optic nerve and reduced integrity of white matter pathways within the optic radiations • Commonly presents with unilateral proptosis, loss of visual acuity, visual field abnormalities, strabismus, relative afferent pupillary defect, and optic disc edema or atrophy[2]
Chiasm	• May cause precocious puberty (affects hypothalamus); visual acuity and visual field defects can occur. Rarely, obstructive hydrocephalus[2]
Postchiasmatic	• More aggressive clinically than other 2 locations[2]



OPG in left optic nerve
Red asterisk denotes OPG

1. Hirbe AC, Gutmann DH., *Lancet Neurol*. 2014;13(8):834-843; 2. Campen CJ, Gutmann DH., J Child Neurol. 2018;33(1):73-81; 3. Listernick R, et al., Ann Neurol. 2007;61(3):189–191; 4. Blanchard G, et al., Eur J Paediatr Neurol. 2016;20(2):275–281; 5. Guillamo SJ, et al., Brain. 2002;126(1):152–160; 6. Dalla Via P, et al., Neuro-Oncol. 2007;9(4):430–437.

NF1 is Associated With a Risk of Cancer in Paediatric and Adult Patients

~60% lifetime risk of cancer in individuals with NF1*,[1]

Decreased life expectancy is associated with the development of malignant neoplasms[2]

MPNST are the most frequent cause of mortality in NF1[4]

Cancers	Lifetime Risk[3]
Glioma of the optic pathway	15%–20%
Plexiform Neurofibromas	30%–50%
Other brain tumour	More than 5-fold increase
Malignant peripheral nerve-sheath tumour	8%–16%
Gastrointestinal stromal tumour	4%–25%
Breast cancer	About 5-fold increase
Leukaemia	About 7-fold increase
Pheochromocytoma	0,1%–5,7%
Duodenal carcinoid tumour	1%
Rhabdomyosarcoma	1,4%–6%

*This was observed according to a retrospective analysis to identify patients with NF1 using electronic hospital registers, which included every medical specialty in all secondary and tertiary medical centres in Finland from January 1, 1987 through December 31, 2011. Confirmed patients were observed for cancer diagnoses from their first hospital visit for NF1 after 1987 through death, emigration or through December 31, 2012.[1]

1. Uusitalo E, et al.. *J Clin Oncol.* 2016;34(17):1978-1986. 2. Hirbe AC, et al. *Am Soc Clin Oncol Educ Book*. 2024;44(3):e432242. 3. Landry JP, et al. *JAMA Netw Open.* 2021;4(3):e210945. 4. Duong TA, et al. *Orphanet J Rare Dis*. 2011;6:18.

PNF- related mortality:

J Pediatr. 2012 Mar;160(3):461-7. doi: 10.1016/j.jpeds.2011.08.051. Epub 2011 Oct 11.

Pediatric plexiform neurofibromas: impact on morbidity and mortality in neurofibromatosis type 1

Carlos E Prada [1], Fatima A Rangwala, Lisa J Martin, Anne M Lovell, Howard M Saal, Elizabeth K Schorry, Robert J Hopkin

There is an increased risk of additional tumors and mortality associated with symptomatic PNF[1]

154 children with NF1 and PNF

Children with symptomatic PNF had a higher mortality rate (3.2%) compared to patients without PNF or with asymptomatic PNF (0.5%)

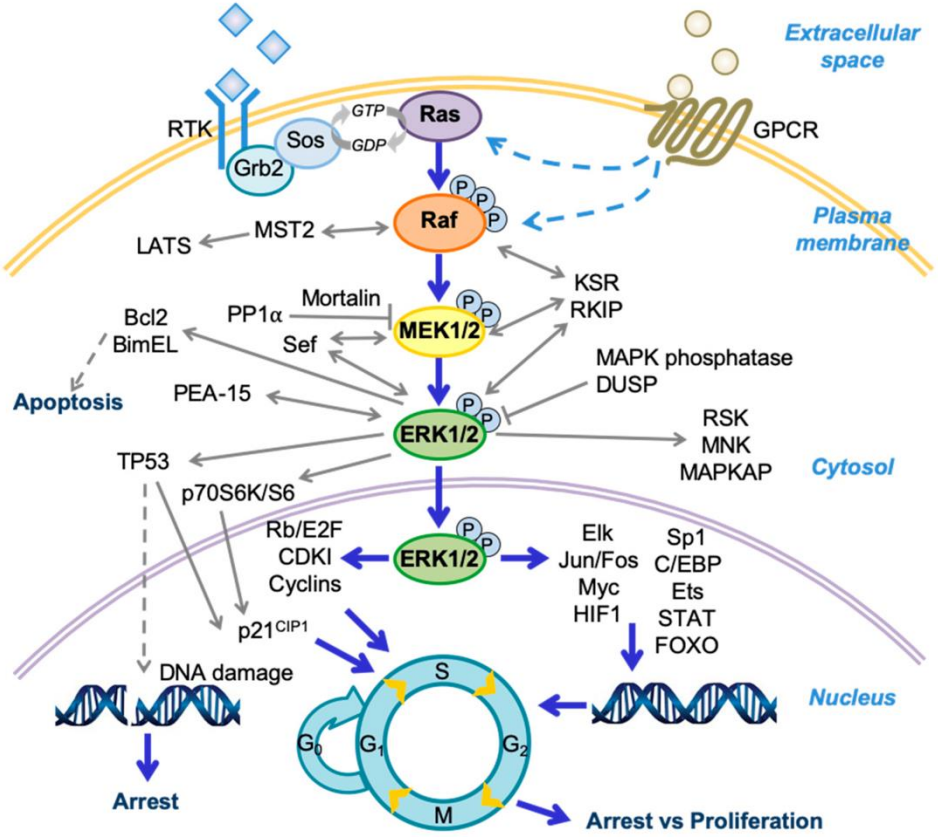
The most common morbidities leading to surgical interventions were neurological, disfiguring, orthopedic, and airway-related issues

1.Prada CE et al., J Pediatr. 2012 Mar;160(3):461-7

Plexiform Neurofibromas

- In PNs, Schwann cells express cytokines and growth factors that cause an increase in Ras-GTP-mediated intracellular signalling cascades within the cell
- **Following the activation of RAS, the Raf/MEK/ERK-activated mitogenic protein kinase (MAPK) pathway and numerous other cell signalling pathways are activated, altering many aspects of Schwann cell function (cell growth, proliferation, migration, differentiation and survival)**
- Moreover, ERK remains activated above baseline levels for weeks, resulting in prolonged inflammation and abnormal resolution of the lesion

Raf/MEK/extracellular signal-regulated kinase (ERK) pathway and its regulators and effectors[1]

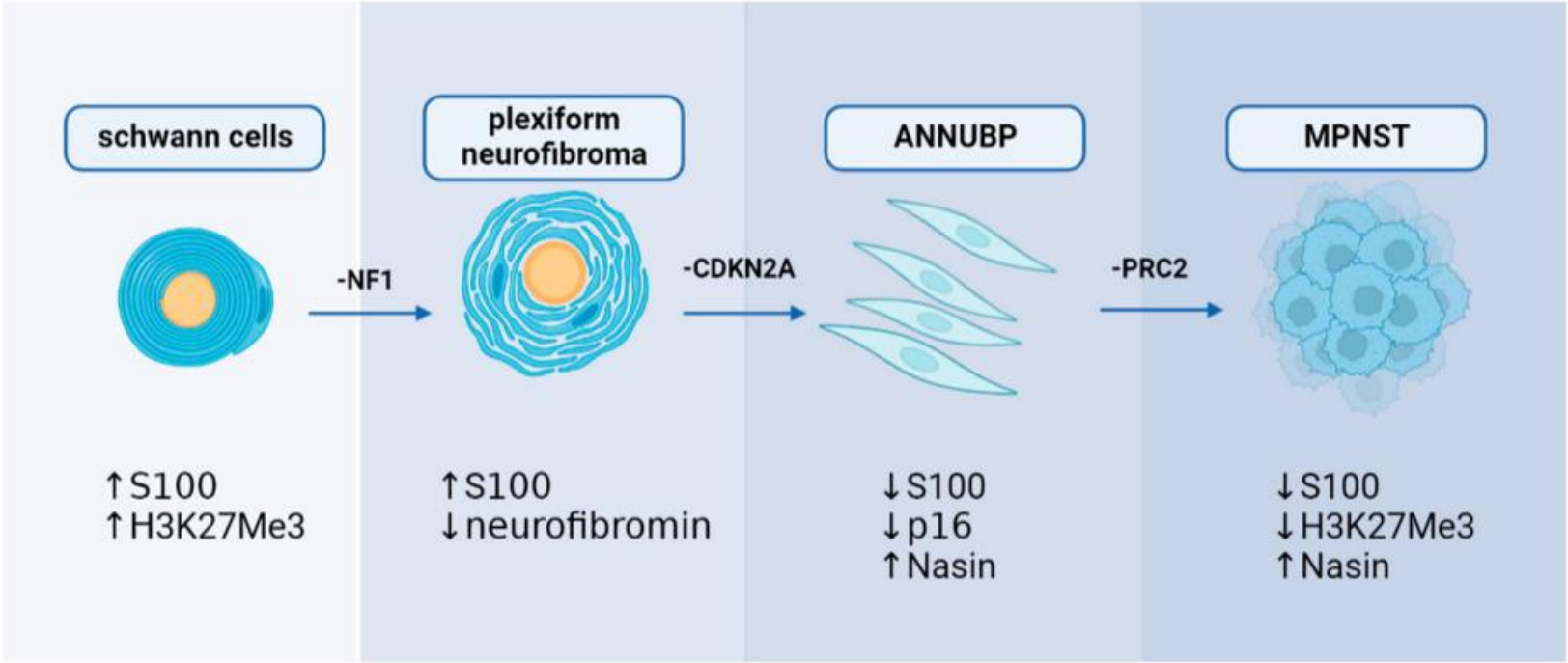


Modified by Wu, P.-K et al[1]

1. Wu, P.-K et al., *Int. J. Mol. Sci.* 2020, *21*, 5436

To transform a benign lesion (neurofibroma) into a malignant tumor, **additional genetic alterations are required** (including **deletions** or **mutations** in key **regulatory genes** such as CDKN2A or TP53), which work in synergy to drive disease progression

Malignant peripheral nerve sheath tumor (MPNST) requires a sequential accumulation of genetic mutations alongside the initial NF1 loss[1,2]



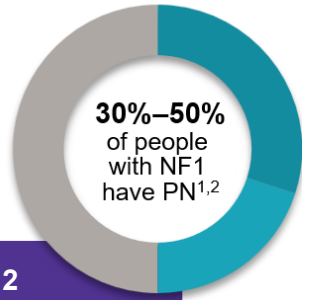
Modified by Yao C et al[2]

1. Zhang X, et al. *Genes (Basel)*. 2020;11(3):287; 2. *Yao C et al., Cancers (Basel). 2023 Feb 8;15(4):1077*

Plexiform Neurofibromas: Overview & Clinical Presentation

Overview of Plexiform Neurofibromas

- **Benign multicellular neoplasms of the neurovascular plexuses.** They involve multiple nerve fibre bundles and consist of numerous cells (Schwann cells, fibroblasts, mast cells, perineural cells, and macrophages)
- There is variable usage and some confusion regarding the distinction between plexiform neurofibroma and diffuse cutaneous neurofibroma; **plexiform neurofibromas are deeper lesions affecting nerves and plexuses**
- **A frequent and almost exclusive complication of NF1**
- They may be congenital[5,6]
- **A quarter of individuals with NF1 have visible or symptomatic PNs**, and MRI shows that >50% have at least one PN[1–4]
- **They grow more rapidly in the first decade of life** and taper off in late adolescence[7,8]
- **Variable symptoms/morbidity (location/size/age)–asymptomatic**[9]
- **Risk of malignant degeneration (8-13% MPNST)** [10,11]



Plexiform Neurofibroma[9,12]



Left: Large diffuse PN on the right leg of woman with NF1[9]
Right: MRI scan of an intra-abdominal PN (denoted by asterisk)[12]

Adapted from Gutmann DH, et al. Nat Rev Dis Primers. 2017; Jett K, et al. Genet Med. 2010.

1. Poplausky D, et al. *Cancers*. 2023;15(2770). 2. Hirbe A, et al. *Lancet Neurol*. 2014;13(8):834-843. 3. Prada CE, et al. *J Pediatr*. 2012;160(3):461-467. 4. Miller DT, et al. *Pediatrics*. 2019;143(5):e20190660. 5. Nguyen R, et al. *Genet Med*. 2013;15(9):691-697. 6. Packer RJ, et al. *J Child Neurol*. 2018;33(1):82-91. 7. Nguyen R, et al. *Orphanet J Rare Dis*. 2012;7(75). 8. Pemov A, et al. *Oncogene*. 2017;36(22):3168-3177. 9. Gutmann DH, et al. *Nat Rev Dis Primers*. 2017;3:17004. 10. Evans DG, et al. *J Med Genet*. 2002;39(5):311-314. 11. Miettinen MM, et al. *Hum Pathol*. 2017;67:1-10. 12. Jett K, et al. *Genet Med*. 2010;12(1):1-11.

Characteristics and Natural History

Neurological Sciences (2022) 43:1281–1293
https://doi.org/10.1007/s10072-021-05361-5

ORIGINAL ARTICLE

Epidemiological and clinical burden associated with plexiform neurofibromas in pediatric neurofibromatosis type-1 (NF-1): a systematic literature review

Ike Iheanacho[1] · Hyun Kyoo Yoo[2] · Xiaoqin Yang[3] · Sophie Dodman[1] · Rachel Hughes[1] · Suvina Amin[2]

Asymptomatic and symptomatic PNs often coexist in the same individual

In children, >60% of PNs are symptomatic and are mainly located in the head/neck area
Other sites include the extremities, bladder, intestine, mediastinum, and spine

Dermatological features may provide clues to the presence of PN, including **thickening of the dermis or the presence of coarse hair or hyperpigmentation**

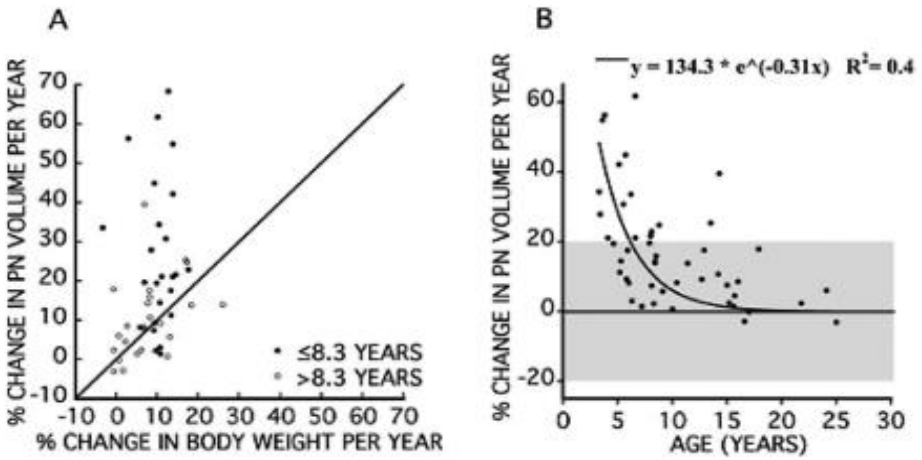
No significant differences in estimated PN growth rates have been found in relation to tumour location, patient sex, race, concomitant pregnancy, or hormonal changes associated with puberty

HIGHLIGHT

NF1 plexiform neurofibroma growth rate by volumetric MRI

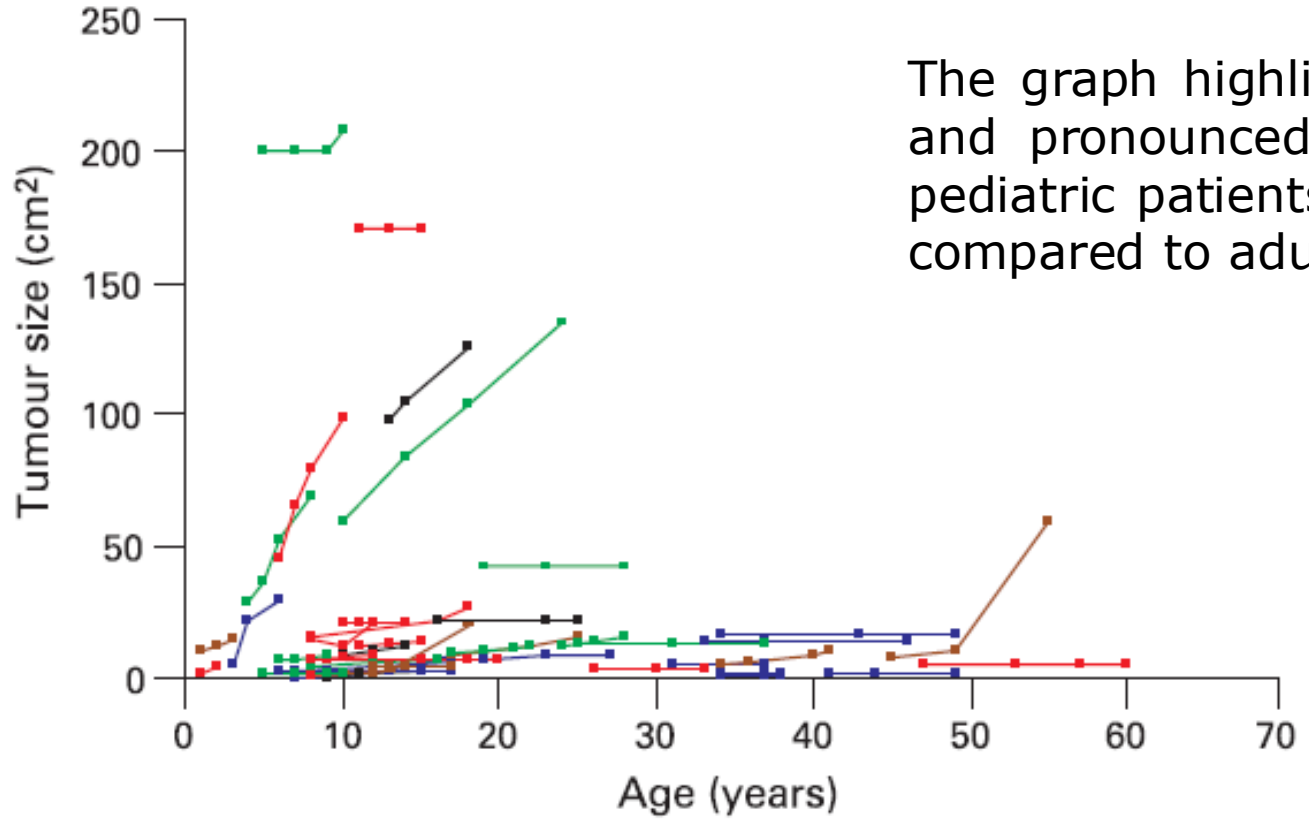
Relationship to age and body weight

E. Dombi, MD; J. Solomon, PhD; A.J. Gillespie, RNMS; E. Fox, MD; F.M. Balis, MD; N. Patronas, MD; B.R. Korf, MD, PhD; D. Babovic-Vuksanovic, MD; R.J. Packer, MD; J. Belasco, MD; S. Goldman, MD; R. Jakacki, MD; M. Kieran, MD; S.M. Steinberg, PhD; and B.C. Widemann, MD



Younger age is associated with faster tumour growth

Tumour size by age in 44 plexiform neurofibromas in 34 patients with NF1[1]



The graph highlights a more rapid and pronounced tumor growth in pediatric patients (under 13 years) compared to adulthood

Key to graphs: red = deep and invasive; blue =deep and displacing; green = superficial and displacing; brown =superficial and invasive; black = superficial only

Modified by Tucker T et al[1]

1.Tucker T et al., J Med Genet. 2009 Feb;46(2):81-5

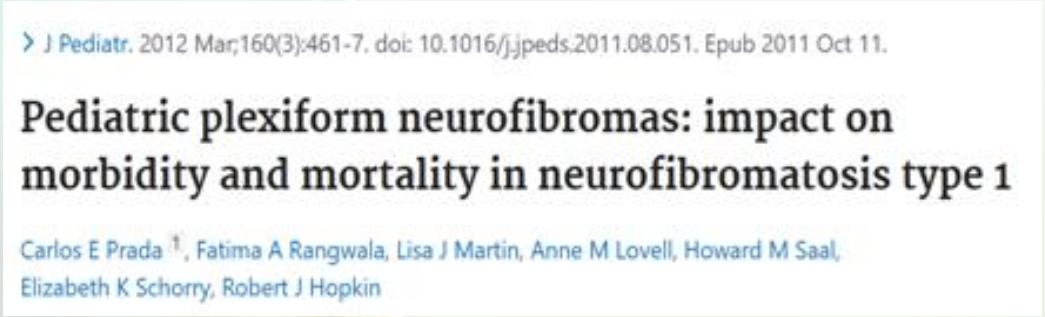
Symptoms

Depending on their location, PNs can cause a wide variety of symptoms, including **vision or hearing problems, airway obstruction, speech and swallowing difficulties, motor dysfunction, bowel or bladder dysfunction, disfigurement, and other symptoms**

The most common symptoms related to PN are pain and motor dysfunction

PN-related morbidities are primarily caused by direct impact on surrounding structures and can be life-threatening when compressing vital organs
Tumour size affects the severity of PN-related symptoms

These functional disabilities have a negative impact on overall quality of life (QOL) for individuals with NF1
Natural history studies indicate that **one-third of children and adolescents with NF1-PN experience socio-emotional difficulties such as anxiety, depression, and social withdrawal, with greater disease severity associated with worse internalising problems and poorer quality of life**


J Pediatr. 2012 Mar;160(3):461-7. doi: 10.1016/j.jpeds.2011.08.051. Epub 2011 Oct 11.

Pediatric plexiform neurofibromas: impact on morbidity and mortality in neurofibromatosis type 1

Carlos E Prada [1], Fatima A Rangwala, Lisa J Martin, Anne M Lovell, Howard M Saal, Elizabeth K Schorry, Robert J Hopkin


Neuro-Oncology
20(12), 1643–1651, 2018 | doi:10.1093/neuonc/noy067 | Advance Access date 28 April 2018

Association of plexiform neurofibroma volume changes and development of clinical morbidities in neurofibromatosis 1

Andrea M Gross, Gurbani Singh, Srivandana Akshintala, Andrea Baldwin, Eva Dombi, Somto Ukwuani, Anne Goodwin, David J. Liewehr, Seth M. Steinberg, and Brigitte C. Widemann

NF1-PN significantly impacts patient HRQoL, pain, and mental health beyond just tumor growth

- NF1-PN presents a **diverse and multifaceted burden**, with wide-ranging experiences across **pediatric and adult stages**
- Overall QoL in patients with PN is directly related to **disease complications and pain interferes with daily activities**
- **59% of pediatric patients** (aged 6-18 years) and **73%** of **caregivers** report that **pain interferes with daily functioning,** regardless of prescription or OTC analgesic medication use, showing clear unmet need[1]



Pain Burden: patients ages 6-18 years with NF1-PN experienced pain interference to a degree that correlated with total tumor volume[2]



Pain Treatment Gap: no specific approved therapy for NF1-related pain[3]. Current approaches include:

- Analgesics (OTC and opioids)
- Neuropathic agents (e.g., gabapentin)
- Surgical intervention in selected cases

Overall efficacy remains **incomplete and inconsistent**



Mental health[4]:

- Children with NF1 have a higher prevalence of **anxiety disorders** than the general pediatric population
- Adults with NF1 have increased rates of depression and anxiety
- Visible PNs can **impact self-esteem** and self-confidence

Key Patient and carer Concerns



Concerns reported by patients and caregivers are consistent and rank in similar order of prominence across studies[2]:

Patients (5–18 years)	Parents of affected patients
Top concerns, in order of prominence:	**Primary concerns include:**
1. Pain / discomfort	1. Physical functioning
2. Functional limitations (activity and daily role)	2. Pain / discomfort
3. Appearance / disfigurement	3. Appearance / disfigurement
4. Stigma	4. Social and relationship difficulties
5. Anxiety	5. Activity limitations

1. Wolters PL, Burns KM, Martin S, et al., Am J Med Genet A. 2015;167A(9):2103-2113; 2. Lai JS, Jensen SE, Patel ZS, et al., Am J Med Genet A. 2017;173(1):79-87; 3. Gutmann DH, Ferner RE, Listernick RH, et al., *Nat Rev Dis Primers*. 2017;3:17004.; 4. Vogel AC, Gutmann DH, Morris SM.,*Dev Med Child Neurol*. 2017;59(11):1112-1116

Indications to treatment



Careful selection of treatment versus observation for PN is important to maximise benefits and minimise risks

The goal of treatment is to improve or prevent morbidity associated with PNs

Several factors must be considered: **the age of the patient** (young children are more likely to have growing PN), whether the PN is causing or likely to cause **morbidity,** or whether it is showing progressive growth. The larger the tumour, the more likely it is to cause morbidity[1]

The presence of morbidity, especially if refractory to symptomatic treatment, is the most relevant criterion to consider. In addition, **individuals with PNs adjacent to or compressing structures such as the spinal cord or airways may not be symptomatic but are at risk of future morbidity if the tumour grows[2]**

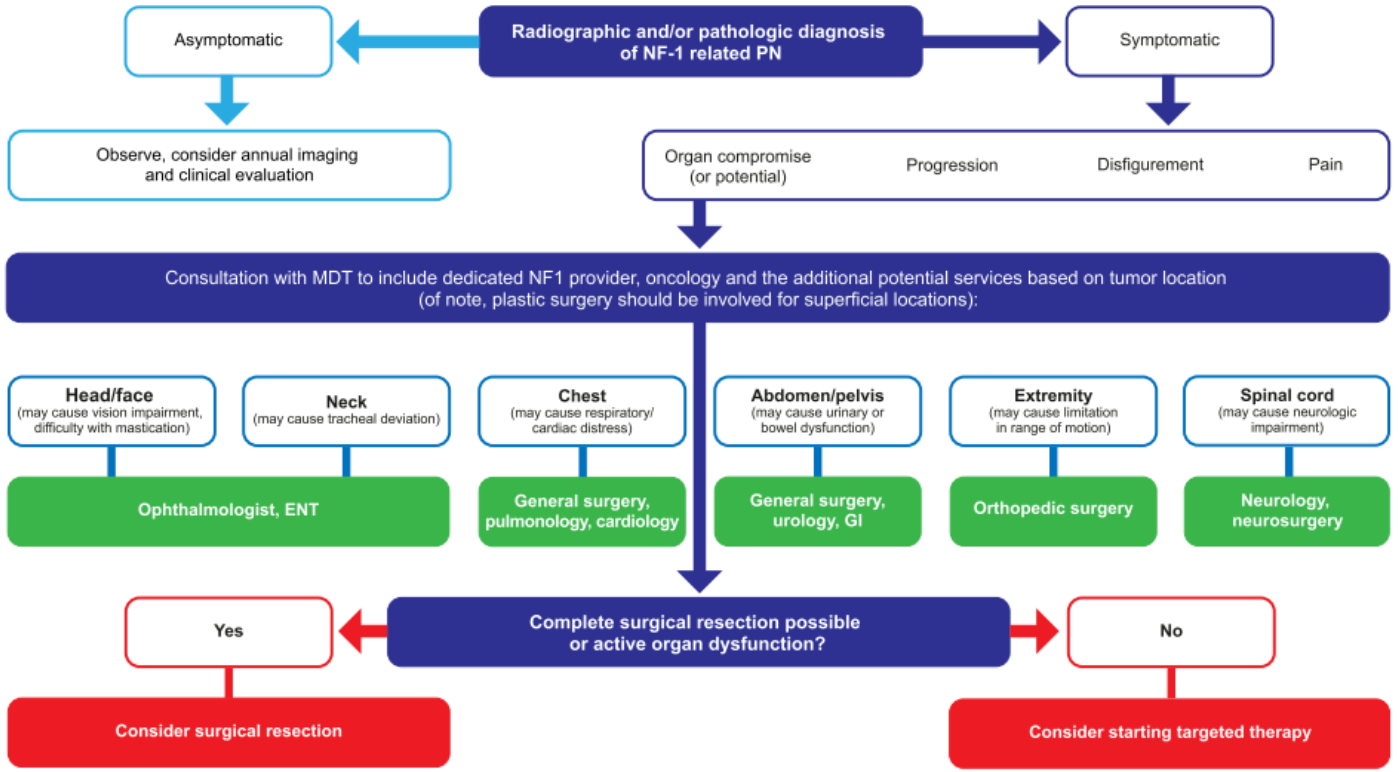
However, PNs growth must be assessed in the context of its growth rate and present/imminent morbidity. For example, a tumour that slowly increases in size without actual or imminent morbidity may warrant observation[1]

1.Fisher MJ et al., Neuro Oncol. 2022 Nov 2;24(11):1827-1844; 2.Armstrong AE et al., Neuro Oncol. 2026 Apr 1;28(4):847-863

Indications to treatment...who decides?

Given the complexity of the clinical presentation and treatment of PNFs, it is useful to have a **multidisciplinary team** that includes **paediatricians, neurologists, geneticists, surgeons, neuropsychiatrists, ophthalmologists, psychologists, cardiologists, urologists, pulmonologists, neuroradiologists, pathologists, neurosurgeons, dermatologists, physiatrists, oncohaematologists, plastic surgeons, maxillofacial surgeons, orthopaedic surgeons, and paediatricians in the patient's area**

Multidisciplinary team management of patients with NF1-PN[1]



Modified by Armstrong AE et al[1]

1.Armstrong AE et al., BMC Cancer. 2023 Jun 16;23(1):553

Importance of a Multidisciplinary Care Team

Guidelines,* such as ERN GENTURIS, emphasize the importance of a multidisciplinary care team for NF1 care[1–3]

Specialties involved include, but are not limited to:



Role of the NF1 Specialty Clinic

- Diagnose NF1 in difficult cases[1]
- Determine treatment path for PN[2]
- Monitor and manage complex disease[1]
- Educate and support the patient and family[1]

ERN GENTURIS, European Reference Network Genetic Tumor Risk Syndromes; NF1, neurofibromatosis type 1, PN, plexiform neurofibroma.
*Consensus recommendations were developed in the United Kingdom, United States and European Union.[1–3]

1. Ferner RE, et al. *J Med Genet.* 2007;44(2):81-88. 2. Fisher MJ, et al. *Neuro Oncol*. 2022;24(11):1827-1844. 3. Carton C, et al. *eClinicalMedicine.* 2023;56e101818.

Monitoring Guidelines for Pediatric Patients with NF1

Consensus recommendations from ERN GENTURIS, a panel of multidisciplinary NF1 experts and clinical practice resources
All pediatric patients with uncomplicated NF1 should be assessed once annually, ideally at a multidisciplinary clinic, for the following:[1–3]



- Development and progress at school
- Measurement of head circumference
- Pubertal development, including height and weight



- Cardiovascular health
  - Congenital heart disease, especially pulmonary stenosis



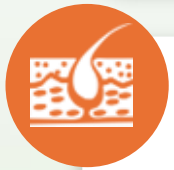
- Visual symptoms
  - Visual acuity and fundoscopy until age 7 years
  - Optic pathway glioma* and glaucoma



- Scoliosis and underlying PNs



- Blood pressure
  - Consider renal artery stenosis, pheochromocytoma



- Skin
  - Cutaneous neurofibroma, subcutaneous and PNs

ERN GENTURIS, European Reference Network Genetic Tumor Risk Syndromes; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.
*Asymptomatic pediatric patients should also have 1 baseline assessment of color vision and visual fields at the appropriate developmental age.1

1. Ferner RE, et al. *J Med Genet*. 2007;44(2):81-88. 2. Miller DT, et al. *Pediatrics*. 2019;143(5):e20190660. 3. ERN GENTURIS. Tumor Management in Neurofibromatosis Type 1 Guideline. January 18, 2023. Accessed July 21, 2025. https://genturis.eu/l=eng/Guidelines-and-pathways/Clinical-practice-guidelines/Neurofibromatosis-type-1-guideline.html.

General Management Guidelines for Adult Patients

Consensus recommendations from ERN GENTURIS, a panel of multidisciplinary NF1 experts and clinical practice resources
Although most adult NF1-associated issues can be managed by an internist or primary care physician, a multidisciplinary team approach within a specialized NF1 clinic is recommended[1,2]

- Educate patients about the signs and symptoms of MPNSTs at initial and follow-up visits[1]

- Consider whole-body MRI for adolescent and young adult patients aged 16–20 years to assess internal tumor burden, identify PNs, and determine adult patient follow-up regimen[3,4]

- Breast cancer risk is increased, and women with NF1 should begin yearly MRIs (or mammograms, as a second-best alternative) starting at age 30[2]

- Revisit family planning annually[1]
  - Review risk of having a child with the condition
  - Offer information on options, such as contraception
  - Referral for genetic counseling if needed

- Consider screening for depression and anxiety[1,5]

PN

- Manage PNs as clinically indicated[4]

ERN GENTURIS, European Reference Network Genetic Tumor Risk Syndromes; MPNST, malignant peripheral nerve sheath tumor; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.

1. Stewart DR, et al. *Genet Med*. 2018;20(7):671-682. 2. ERN GENTURIS. Tumor Management in Neurofibromatosis Type 1 Guideline. January 18, 2023. Accessed July 21, 2025. https://genturis.eu/l=eng/Guidelines-and-pathways/Clinical-practice-guidelines/Neurofibromatosis-type-1-guideline.html. 3. Evans DGR, et al. *Clin Cancer Res*. 2017;23(12):e46-e53. 4. Fisher MJ, et al. *Neuro Oncol*. 2022;24(11):1827-1844. 5. Julian N, et al. *J Nurse Pract*. 2014;10(1):30-35.

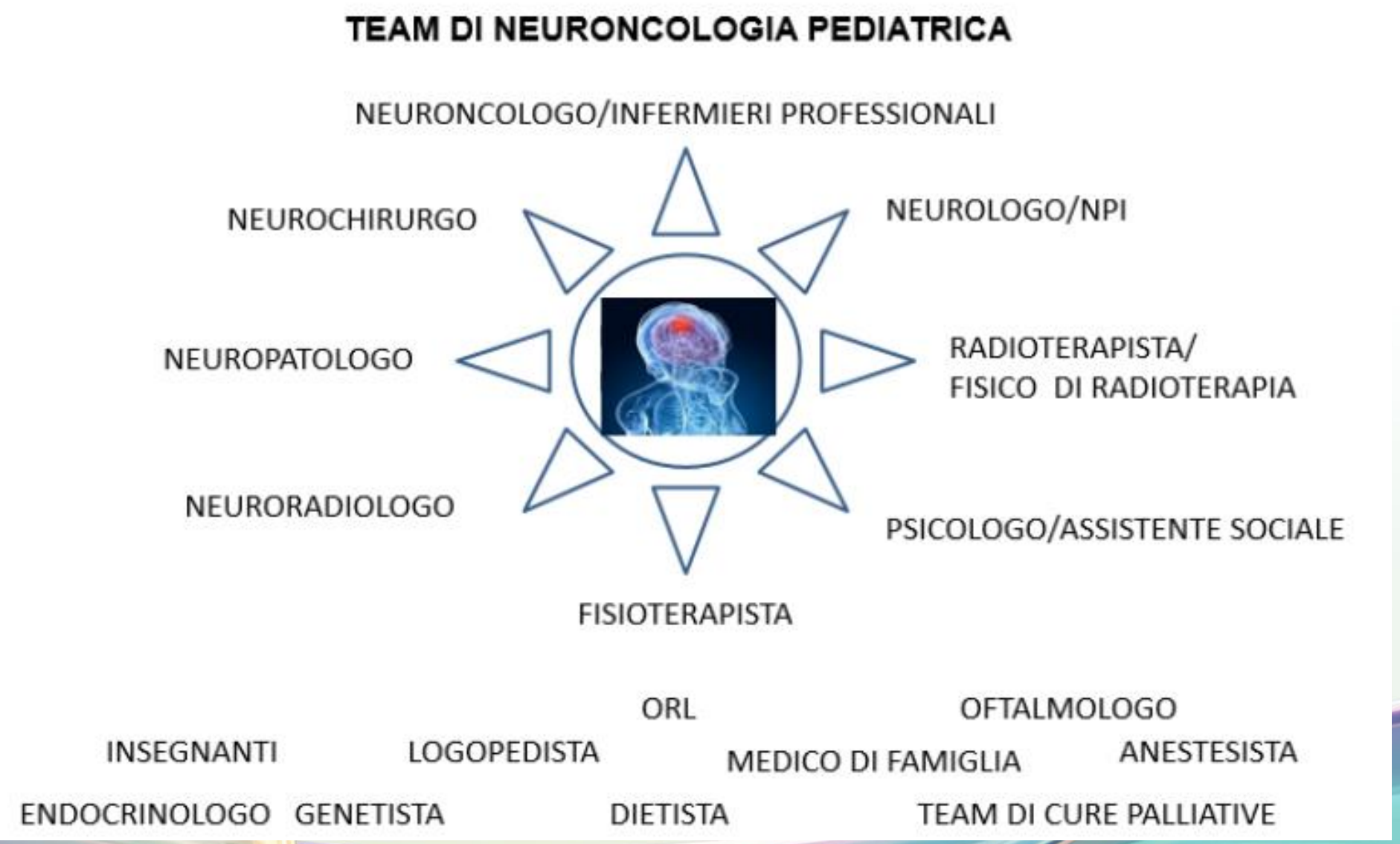
OUR REALITY
NF1 INTERDISCIPLINARY TEAM

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

Diagnostic, Therapeutic, and Care Pathway for the Multidisciplinary Management of Pediatric Patients with Suspected/Confirmed Type 1 Neurofibromatosis

PEDIATRIC NEUROLOGY TEAM COORDINATORS	NF1 DIAGNOSIS AND FOLLOW-UP
DERMATOLOGY	initial identification of diagnostic criteria affecting the skin (café-au-lait spots, lentigines, neurofibromas) and subsequent follow-ups, with particular attention to any changes in the clinical picture
SPINAL SURGERY	identification of diagnostic criteria affecting the musculoskeletal system (sphenoid dysplasia, anterolateral tibial bowing, pseudoarthrosis of long bones) and subsequent follow-ups, with particular attention to the onset of complications (scoliosis, etc.)
OPHTHALMOLOGY	identification of diagnostic criteria affecting the ocular system (Lisch iris nodules, choroidal abnormalities) and subsequent follow-ups, with particular attention to the onset of signs and symptoms indicative of complications (optic pathway glioma, etc.)
RADIOLOGY	For monitoring the onset of neurofibromas affecting internal organs.
CARDIOLOGY	For monitoring the onset of cardiac neurofibromas and any complications (pulmonary valve stenosis, vascular dysplasia, vasculopathy, arterial hypertension, etc.)
GENETICS	For the identification of pathogenic variants in the NF1 gene and subsequent genetic counseling
NEURORADIOLOGY	For the detection and monitoring of the onset of alterations affecting the brain and spine (gliomas, neurofibromas, cerebrovascular alterations, etc.)
ENDOCRINOLOGY	For monitoring any endocrinological complications (delayed growth and weight gain, precocious puberty, etc.).
PEDIATRIC ONCOLOGY	For the monitoring and treatment of oncohematological complications (gliomas, plexiform neurofibromas, etc.)
NEUROSURGERY	For monitoring and treating disorders affecting the brain and spinal cord (gliomas, neurofibromas, cerebrovascular disorders, etc.)

OUR REALITY
PEDIATRIC NEURONCOLOGY TEAM



Current Monitoring Recommendations for NF1-PN

Consensus recommendations from ERN GENTURIS, a panel of multidisciplinary NF1 experts and clinical practice resources

All Individuals Diagnosed with NF1 Should be Assessed for the Presence of PN*

Standard evaluation includes physical exam, neurological exam, and/or patient history[1-5]

FDG-PET with CT has high diagnostic accuracy for detection of MPNST arising in the background of PN[1-3,5,6]

Imaging is important for screening at baseline and for surveillance in individuals with known PN:[1,2]

- Some practitioners, along with ERN GENTURIS guidelines, advocate for baseline whole-body MRI in late adolescence or early adulthood[1,2]

Regional or whole-body MRI is the imaging modality of choice for persons with symptoms or visible PN:[1-3]

- MRI performed without the administration of intravenous contrast material is preferred over CT [1,2]
- Regional MRI allows for evaluating a specific PN in greater detail and is used more often for surveillance of known PN [1,2]
- Whole-body MRI is advantageous for patients with multiple or very large PN[1,2,6]

Adult patient considerations[7]

- Imaging of PN may not be necessary in an asymptomatic lesion involving only subcutaneous tissue

Paediatric patient considerations[8]

- Neuroimaging studies are indicated for head and neck PNs increasing in size or with new development of pain

CT, computed tomography; ERN GENTURIS, European Reference Network Genetic Tumour Risk Syndromes; FDG, ^{18}F-fluorodeoxyglucose; MPNST, malignant peripheral nerve sheath tumour; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; PET, positron emission tomography; PN, plexiform neurofibroma.

*These statements were generated from a literature review, ERN GENTURIS guidelines and country-level guidance in France, the United Kingdom, Germany, Austria and the United States.[1–6]

1. Fisher MJ, et al. *Neuro Oncol*. 2022;24(11):1827-1844. 2. ERN GENTURIS. Tumour Management in Neurofibromatosis Type 1 Guideline. January 18, 2023. Accessed July 21, 2025. https://genturis.eu/l=eng/Guidelines-and-pathways/Clinical-practice-guidelines/Neurofibromatosis-type-1-guideline.html. 3. Bergqvist C, et al. *Orphanet J Rare Dis.* 2020;15(37). 4. Ferner RE, et al. *J Med Genet.* 2007;44(2):81–88. 5. Farschtschi S, et al. *Dtsch Arztebl Int*. 2025;122:71–6. 6. Sunder-Plassmann V, et al. *Wien Klin Wochenschr.* 2024. 7. Stewart DR, et al. *Genet Med*. 2018;20:671-682. 8. Miller DT, et al. *Pediatrics*. 2019;143(5):e20190660.

According to the official **ERN GENTURIS** guidelines, there are currently **no validated molecular or circulating biomarkers (such as blood tests) recommended** in routine clinical practice to predict the growth or malignant progression of neurofibromas[1]

Periodic Clinical Surveillance:

- **Up to 10 years old:** At least **once a year**.
- **11 to 18 years old:** At least **every two years**.
- **Adults:** At least **every three years** (or more frequently for high-risk lesions like plexiform neurofibromas).

Identification of Warning Signs:

- **Persistent pain:** New, deep pain, or pain that wakes the patient at night, without other explanations.
- **Rapid growth:** A sudden increase in volume or a change in texture (the nodule becomes hard or fixed).
- **Neurological deficits:** New onset of tingling, loss of strength, or sensory changes in the area of the affected nerve.

Sequential Diagnostic Imaging Approach:

- **Magnetic Resonance Imaging (MRI / WB-MRI):** The gold standard to define anatomy, volume, and growth over time of plexiform neurofibromas.
- **FDG-PET/CT:** Used as a targeted, second-line test to confirm or rule out malignant transformation when clinical signs or MRI suggest a strong suspicion.

1.Carton C, et al., 2023 EClinicalMedicine. 2023 Jan 13;56:101818

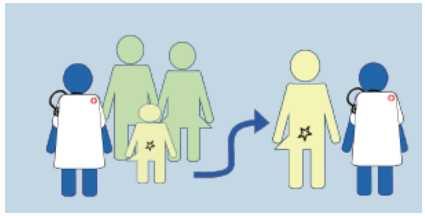
Consensus Expert-Recommended Treatment of NF1-PN by Symptoms and Age[1]

Symptoms	None (not near a vital structure)	None (near a vital structure)	Progression	Pain	Organ Compromise	Deformity
Adults	Observe Consider annual imaging and clinical evaluation	Consider observation with annual imaging and clinical evaluation (low risk for growth)	Consider further imaging and biopsy to evaluate for malignant transformation	*New:* consider further imaging and biopsy to evaluate for malignant transformation *Chronic:* **consider treatment**	Preference for surgical intervention Consider concurrent evaluation for malignant transformation	**Consider treatment** and/or consultation with plastic surgery
Pediatrics	Same as adults	**Consider treatment** (risk for growth)	**Consider treatment** if morbidity is likely with continued growth *Adolescents:* first consider evaluation similar to adults	*New (adolescence):* consider evaluation similar to new onset in adults *Otherwise:* **consider treatment**	Preference for surgical intervention *Adolescents:* also consider concurrent evaluation for malignant transformation	**Same as adults**

1.Armstrong AE, et al. Neuro-Oncol. 2026;28(4):847-863.

ERN GENTURIS guidelines define specific criteria and recommendations for managing the transition from pediatric to adult monitoring in patients with NF1[1,2]

Pediatric treatment guidelines: **optic pathway gliomas**, MPNSTs, **cerebrovascular and congenital heart abnormalities, skin and scoliosi**.



Adult treatment guidelines: optic pathway gliomas, **MPNSTs**, **breast cancer, hypertension, skeletal complications, cutaneous neurofibromas, and neuropathic pain** as well as **depression**, **anxiety** and **family planning**.

Clinical assessment:

- **Up to 10 years old:** At least **once a year**.
- **11 to 18 years old:** At least **every two years**.
- **Adults:** At least **every three years** (or more frequently for high-risk lesions like plexiform neurofibromas).

Transition period: consider more frequent assessments

Imaging and surveillance:

- WB-MRI during transition to assess internal tumor burden and malignant transformation risk.
- MRI of visual pathway.
- OCT or related optic assessments as appropriate.

Increase imaging frequency if progression or new symptoms

Multidisciplinary care:

- Involve NF1-expert team: neurology, oncology, radiology, ophthalmology, genetics, psychosocial support.

NF1, neurofibromatosis type 1; MPNSTs, Malignant peripheral nerve sheath tumor

1.Carton C, et al., 2023 EClinicalMedicine. 2023 Jan 13;56:101818; 2. https://www.genturis.eu/l=eng/Assets/20230118_ERN_GENTURIS_Care_Pathway_NF1_v1.8_accepted-31aug2022.pdf

Barriers to Effective Healthcare Transition



Health System Barriers*

- Limited number of adult clinics and NF1 specialists[1]
- Lack of multidisciplinary teams in adult patient clinics and limited appointment availibility[2]
- Limited knowledge about NF1 care and treatments[2]
- Lack of available services (e.g., nurses, social workers), care coordination, and follow up[2]
- Poor communication about transition from pediatric to adult care[2]
- Inadequate process of transferring medical records[2]

Patient and Parent/Caregiver Barriers

- Lack of knowledge of NF1 and importance of medical care[2]
- Difficulty finding NF1 specialists[2]
- Travel barriers (long distances to clinic sites)[1]
- Emotional burden of disease complications[2]
- Financial concerns (income, insurance coverage) [2]
- Limitations in decision-making abilities or self-advocacy[2]
- Discomfort with parental/caregiver transfer of responsibility[2]
- Psychosocial and development barriers common to adolescent and young adult patients[2]

*Health system barriers will vary from country to country in Europe.[4]

1. Merker VI, et al. *BMC Health Serv Res*. 2018;18(1):668. 2. Radtke HB, et al. *Pediatric Health Med Ther*. 2023;14:19-32. 3. Ellison JL, et al. *J Pediatr Nurs.* 2022;66:70-78. 4. Farschtschi S, et al. *Dtsch Arztebl Int*. 2025;122:71–76.

OUR REALITY

WHAT WE LEARNED FROM THE PAST

There is no strict start for transition (age 17-19)

AYAs often don’t accept transition, expecially in complex clinical cases

Each single case must be avaluated from all points of view (first of all psycological impact) and tailored transition plans must be organized

Strong collaboration between our institution and adult world must be shown to the patient and its family as soon as possible

CONGIUNTE visits are of great help so that transition can occurr slowly and the family can adapt to the new managment nei tempi giusti

OUR REALITY

WHAT WE DO NOW



NF1 without ONCOLOGICAL IMPLICATIONS

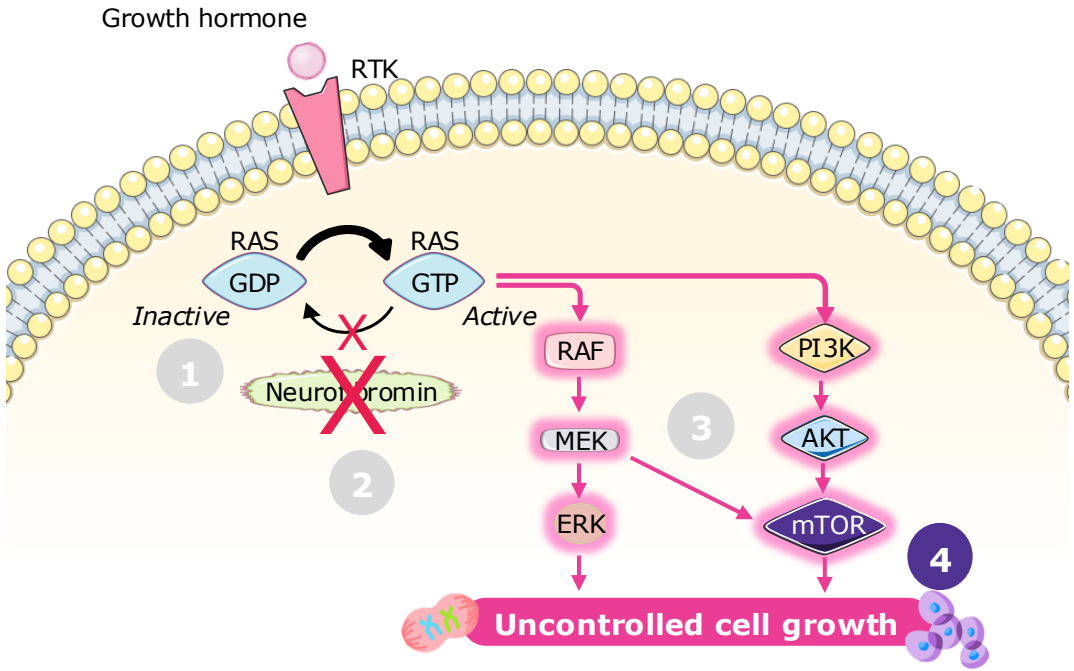
ADULT NEUROLOGIST

NF1 WITH ONCOLOGICAL IMPLICATIONS

ADULT NEURONCOLOGIST

Neurofibromin deficiency causes overactive RAS signaling

Impact of Neurofibromin loss on the RAS / MAPK signaling pathway[1]



1. Neurofibromin is a negative regulator of RAS, accelerating the conversion of active RAS-GTP into inactive RAS-GDP

2. Mutation of the *NF1* gene results in the **loss of neurofibromin**, leading to **activation of RAS** (RAS remains in the GTP-bound active state)

3. **Constitutively active RAS** activates the RAF / MEK / ERK (MAPK) and PI3K / AKT / mTOR signaling pathways

4. The **increased signaling** promotes **uncontrolled cell growth and survival**, contributing to tumor development in NF1-associated diseases and cancers

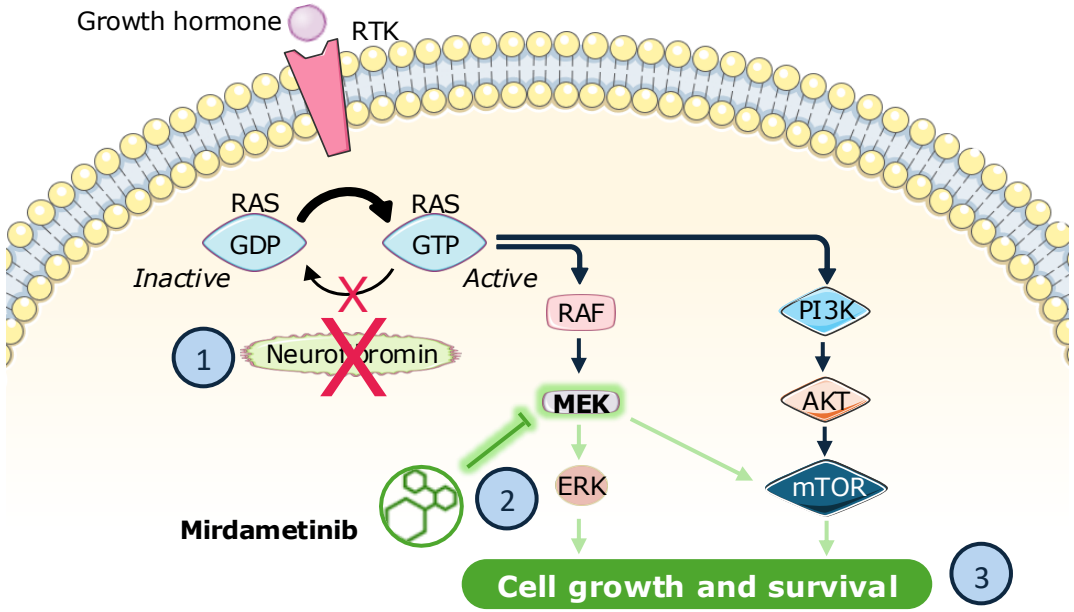
MEK is a key component of the signaling pathways which are **overactive in *NF1* deficient cells**, giving rationale for its inhibition to treat conditions in patients with NF1

1. Gutmann DH, Ferner RE, Listernick RH, et al. Neurofibromatosis type 1. *Nat Rev Dis Primers*. 2017;3:170004.;

Mirdametinib is a highly selective, allosteric, CNS-penetrant MEK1/2 inhibitor that targets the MAPK pathway

- Mirdametinib is an oral, highly selective, potent, CNS-penetrant, non-ATP-competitive allosteric inhibitor of MEK1/2, designed to treat patients with NF1[1-7]
- It targets the **MAPK pathway** by inhibiting phosphorylation and activation of ERK into pERK, inhibiting downstream signaling involved in cellular replication and tumor formation in NF1[8-10]

Mechanism of action (MOA) of mirdametinib



1. **Loss of functional neurofibromin, leads to overactivation of the MAPK pathway which drives cell proliferation and survival[1]**
2. **Mirdametinib inhibits kinase activity of MEK1 and MEK2 and downstream phosphorylation of ERK[2]**
3. **In vitro, this was shown to reduce PN volume and proliferation[2,7]**

By targeting MEK1/2 in the MAPK pathway, mirdametinib is thought to inhibit the phosphorylation of extracellular signal-related kinase (ERK) and the growth of PNs[2,3,7]

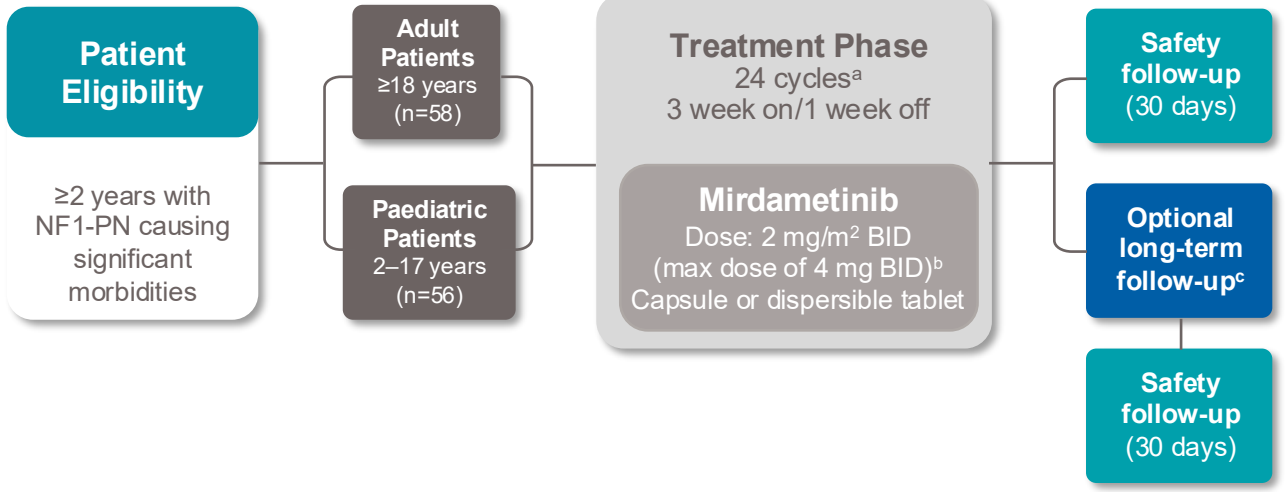
1.de Gooijer MC, Zhang P, Weijer R, Buil LCM, Beijnen JH, van Tellingen O. Int J Cancer. 2018;142(2):381-391; 2.Jousma E, Rizvi TA, Wu J, et al., Pediatr Blood Cancer. 2015;62(10):1709-1716. doi:10.1002/pbc.25546; 3.LoRusso PM, Krishnamurthi SS, Rinehart JJ, et al. Phase I Clin Cancer Res. 2010;16(6):1924-1937; 4.Weiss BD, Wolters PL, Plotkin SR, et al. NF106. J Clin Oncol. 2021;39(7):797-806; 5. Moertel CL, Hirbe AC, Shuhaiber HH, et al. J Clin Oncol. 2025;43:716-729; 6.Gomekli USPI. Accessed July 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219379Orig1s000lbl.pdf; 7.Papale A, Morella IM, Indrigo MT, et al. eLife. 2016;5(e17111); 7. Jessen WJ, Miller SJ, Jousma E, et al. J Clin Invest. 2013;123(1):340-347; 8. Cheng Y, Tian H. 2017;22(10):1551; 9. Harder A. MEK inhibitors Biomark Res. 2021;9(1):26; 10. Klesse LJ, Jordan JT, Radtke HB, et al. Oncol. 2020;25(7):e1109-e1116

Study Design and Key Endpoints for the Multicentre, Open-Label, Pivotal, Phase 2b ReNeu Trial

Study Population[1]

Paediatric (2–17 years) and adult (≥18 years) patients with NF1-PN causing significant morbidities

Trial Design[1,2]



Key Endpoints[d]

Primary

- Confirmed ORR (proportion of patients with ≥20% reduction on MRI of the target PN volume from baseline to Cycle 24, as assessed by BICR on ≥2 consecutive scans within 2–6 months)

Secondary

- DoR
- PROs from baseline to Cycle 13:
  - Worst tumour pain severity (NRS-11)
  - Pain interference (PII)
  - HRQoL (PedsQL)
- Safety and tolerability

AEs: Adverse Events; BICR: Blinded Independent Central Review; BID: Twice a Day; DoR: Duration of Response; HRQoL: Health-Related Quality of Life; Max: Maximum; MRI: Magnetic Resonance Imaging; NCI: National Cancer Institute; NF1: Neurofibromatosis Type 1; NF1-PN: Neurofibromatosis Type 1–Associated Plexiform Neurofibromas; NRS-11: Numeric Rating Scale-11; ORR: Objective Response Rate; PD: Progressive Disease; PedsQL: Pediatric Quality of Life Inventory; PFS: Progression-Free Survival; PII: Pain Interference Index; PN: Plexiform Neurofibromas; PROs: Patient-Reported Outcomes.

Note: To assess the effect of mirdametinib on the natural history of NF1-PN, yearly percent change from baseline in PN volume and PFS were compared between paediatric patients in the ReNeu trial and paediatric patients in the NCI NF1 natural history study. Additionally, mirdametinib–treated paediatric patients with PD at baseline were compared with paediatric patients from the placebo arm of the NCI tipifarnib trial in progressive PN.[1]

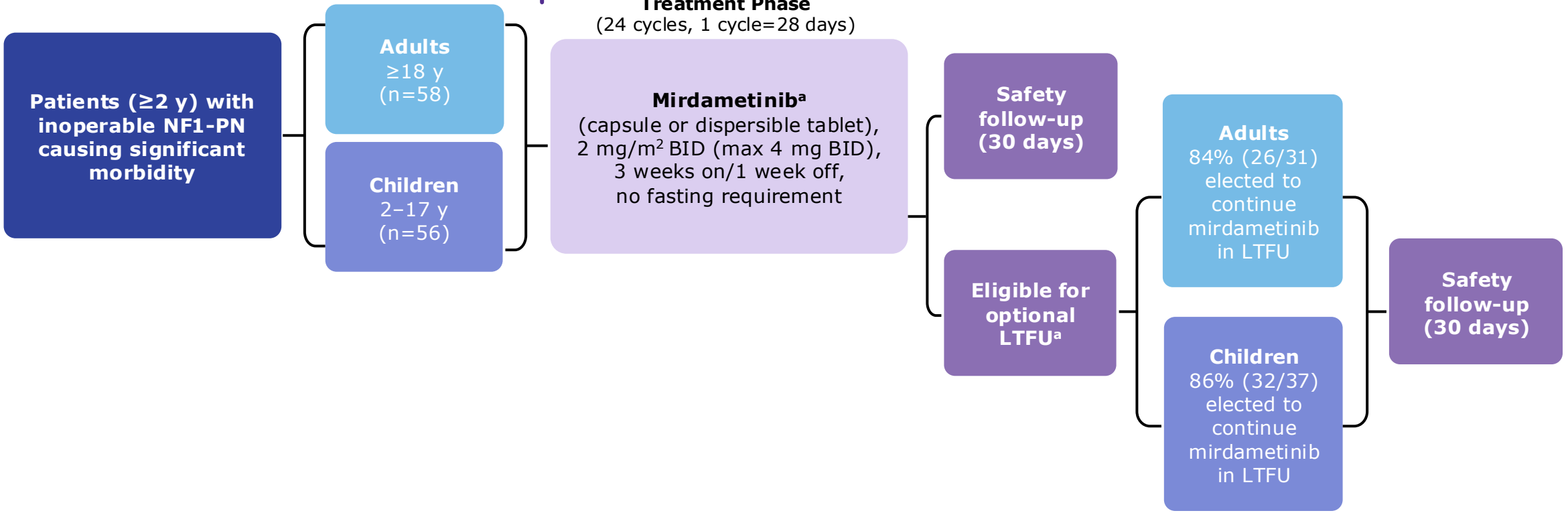
[a]Each cycle was 28 days in duration. [b]There was no fasting requirement. [c]Patients could continue receiving mirdametinib until any of the following occurred: centrally confirmed radiographic disease progression, intolerable AEs, inability to adhere to the protocol or patient- or investigator-determined discontinuation. [d]Endpoints were analysed separately for adult and paediatric patients.[1,2]

1. Moertel CL, et al. *J Clin Oncol.* 2025;43(6):716–729. https://doi.org/10.1200/JCO.24.01034. 2. Oral Presentation: Moertel CL, et al. 2024 ASCO Annual Meeting; May 31–June 4, 2024; Chicago, IL, US.

ReNeu: Pivotal, Phase 2b Trial of Mirdametinib in Adults and Children With NF1-PN (NCT03962543) — Long-Term Analysis From the July 1, 2025, Data Cutoff

Long Term Analysis[1]

Summarizes an additional **~2 years** of data from the September 20, 2023, data cutoff:
- Confirmed ORR and change in target PN volume cumulative from baseline for years 1 through 4
- TRAE rates from individual years 1 through 4



[a]In the LTFU, patients continued on mirdametinib at the last dose assigned in the treatment phase. [b]Per REiNS criteria. Consecutive scans for confirmation of objective response had to occur within 2-6 months. BICR with 2 reviewers and 1 adjudicator. BICR, blinded independent central review; BID, twice a day; LTFU, long-term follow-up; MRI, magnetic resonance imaging; NF1, neurofibromas type 1; ORR, objective response rate; PN, plexiform neurofibroma; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis.

1.Moertel CL, et al. *J Clin Oncol.* 2025;43(6):716-729.

Take Home Messages

- Plexiform neurofibromas can cause important morbidity and negatively affect quality of life
- Given the natural history, all cases of symptomatic/growing and potentially symptomatic PNs must be selected for medical therapy
- A multidisciplinary approach represents the gold standard for treating PNs
- MEK inhibitors are a viable option for treating PNs
- Timely and accurate collection of functional, psychological and radiological data is essential for real world experience

Grazie per l’attenzione