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HEALTHCARE EDUCATION

THE MEKTRIX

DECODING THE REAL-WORLD IMPACT OF THERAPEUTIC ADVANCES IN NEUROFIBROMATOSIS TYPE 1–ASSOCIATED PLEXIFORM NEUROFIBROMA MANAGEMENT ACROSS PEDIATRIC AND ADULT POPULATIONS

This program is supported through an independent educational grant from SpringWorks Therapeutics, Inc.



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OCN
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Symptom Management, Palliative Care, Supportive Care
Treatment

AOCNP
Care Continuum
Professional Practice/Performance
Psychosocial Dimensions of Care
Roles of the APRN
Symptom Management, Palliative Care, Supportive Care
Treatment

BMTCN
Professional Practice/Performance

CBCN
Care Continuum
Oncology Nursing Practice
Psychosocial Dimensions of Care
Treatment

CPHON
Care Continuum
Care of the Pediatric Hematology and Oncology Patient
Disease Related Biology
Health Maintenance
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Disclosures

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Consultant—Aadi Subsidiary Inc., Alexion Pharmaceuticals Inc., AstraZeneca, and SpringWorks Therapeutics Inc.

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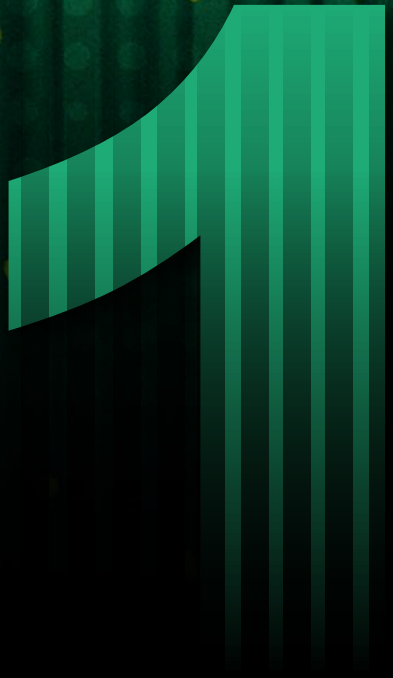
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All identified conflicts of interest have been mitigated.

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LEARNING OBJECTIVE



Assess neuro-oncologic features of neurofibromatosis type 1, including tumor types and neurological signs, to support early recognition and inform clinical decision-making

LEARNING OBJECTIVE

2

Evaluate the use of MEK inhibitors in the management of neurofibromatosis type 1–associated plexiform neurofibromas in pediatric and adult patients, including team-based care to manage adverse events

LEARNING OBJECTIVE



Develop evidence-based, interprofessional care plans for pediatric and adult patients with neurofibromatosis type 1 that reflect current clinical standards and support individualized, longitudinal management

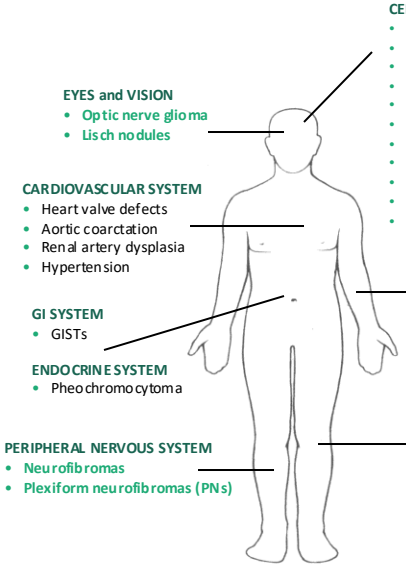
Neurofibromatosis Type 1

Clinical Features and Diagnostic Criteria

The Neurofibromatoses

NEUROFIBROMATOSIS TYPE 1 (NF1)

1 in 2,800 people worldwide



CENTRAL NERVOUS SYSTEM
- Gliomas
- Seizures
- Learning disabilities
- Attention deficit
- Autism
- Headaches
- Precocious puberty
- Vascular abnormalities (Moyamoya)
- Aqueductal stenosis
- Sleep disturbances
- Multiple sclerosis

EYES and VISION
- Optic nerve glioma
- Lisch nodules

CARDIOVASCULAR SYSTEM
- Heart valve defects
- Aortic coarctation
- Renal artery dysplasia
- Hypertension

SKIN
- Café-au-lait macules
- Skinfold freckling
- Juvenile xanthogranulomas
- Melanoma

GI SYSTEM
- GISTs

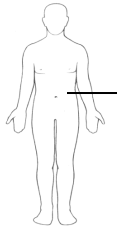
ENDOCRINE SYSTEM
- Pheochromocytoma

SKELETAL SYSTEM
- Dysplasia of long bones
- Pseudarthrosis
- Sphenoid wing dysplasia
- Dystrophic scoliosis
- Scalloping of vertebrae
- Pectus excavatum
- Macrocephaly
- Short stature
- Osteoporosis

PERIPHERAL NERVOUS SYSTEM
- Neurofibromas
- Plexiform neurofibromas (PNs)

NON-NF2 SCHWANNOMATOSIS

1 in 158,000 people worldwide

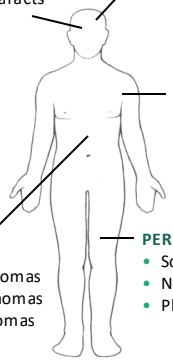


PERIPHERAL NERVOUS SYSTEM
- Spinal schwannomas
- Peripheral schwannomas

PAIN

NF2-RELATED SCHWANNOMATOSIS (NF2)

1 in 67,700 people worldwide



EYES and VISION
- Epiretinal membranes
- Retinal hamartomas
- Juvenile cataracts

CENTRAL NERVOUS SYSTEM
- Meningiomas
- Cranial nerve schwannomas

SKIN
- Schwannomas
- Café-au-lait macules

SPINE
- Schwannomas
- Ependymomas
- Meningiomas

PERIPHERAL NERVOUS SYSTEM
- Schwannomas
- Neurofibromas
- Plexiform schwannomas

GIST, gastrointestinal stromal tumors.

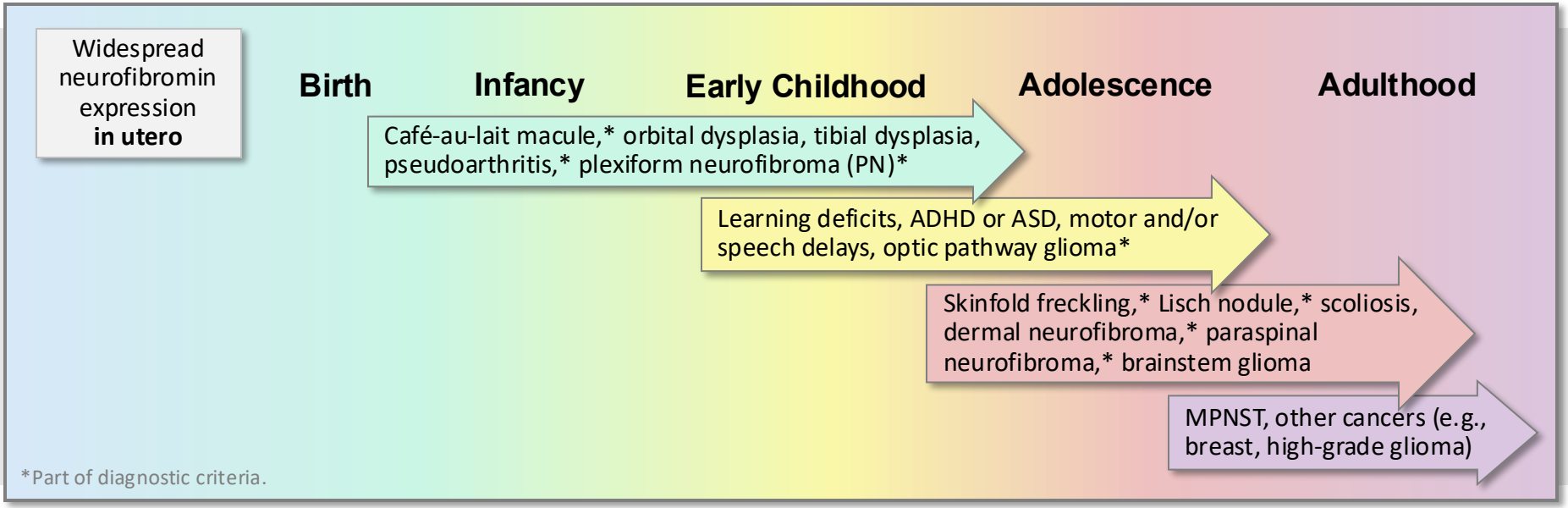
Friedman JM. Neurofibromatosis 1. In: *GeneReviews*. Updated April 3, 2025. https://www.ncbi.nlm.nih.gov/books/NBK1109/.
Moodley M, et al. *Semin Pediatr Neurol*. 2024;52:101172. Lee TJ, et al. *Orphanet J Rare Dis*. 2023;18(1):292.

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Development of Clinical Features of NF1

Timing and Severity Varies

Neurofibromin expression largely restricted to the nervous system and adrenal medulla, with little or no expression in other tissues



ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; MPNST, malignant peripheral nerve sheath tumors.

Kerashvili N, et al. *Expert Rev Neurother*. 2024;24:409–420. Botero V, et al. *J Neurodev Disord*. 2024;16:49.

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NF1
Abnormalities in Skin Pigmentation

Café-au-lait Macules



- Often first sign of NF1
  - May be present at birth and can continue to develop and/or darken over time
  - By 1 year of age, 80% have ≥6 macules
- Not markers of severity
- Present in ~90% of patients with NF1

Skinfold Freckling



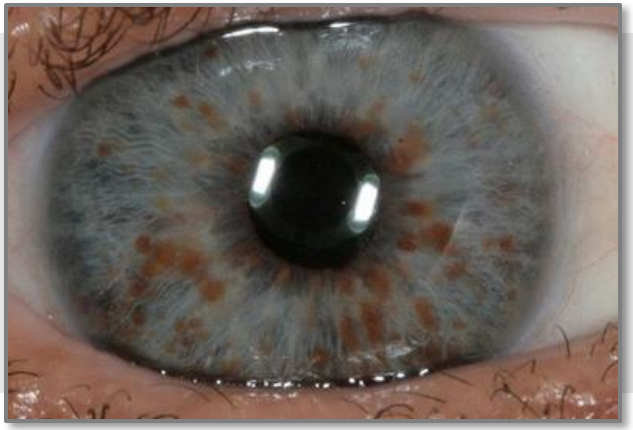
- Present in ~75% of patients
- Usually detected by 5–8 years of age

Lalvani S, et al. *J Multidiscip Healthc.* 2024;17:1803–1817.
Kerashvili N, et al. *Expert Rev Neurother.* 2024;24:409–420. Botero V, et al. *J Neurodev Disord*. 2024;16:49.

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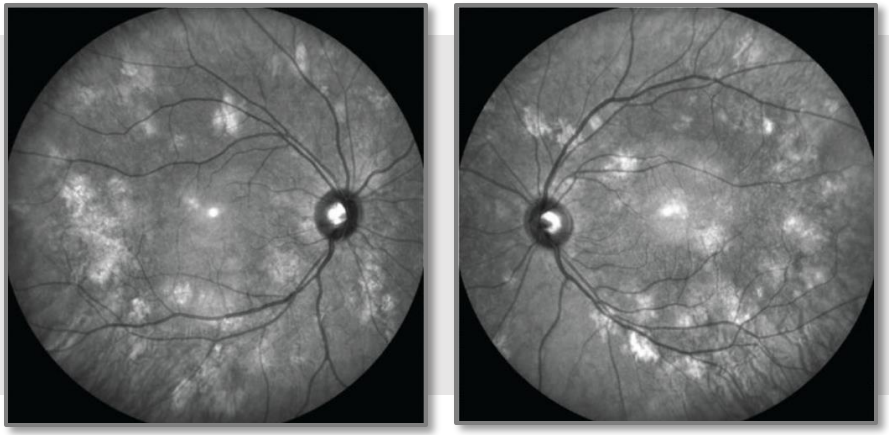
NF1
Ocular Abnormalities

Lisch Nodules



- Present in nearly all patients with NF1
  - Rarely in infants
  - No effect on vision
- Identification requires slit-lamp examination

Choroidal Abnormalities



NIR imaging

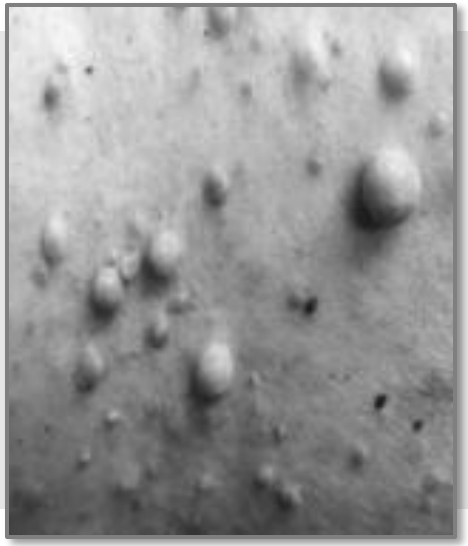
- Present in >64% of patients
  - May be found at earlier ages
  - Asymptomatic
  - Appearance and dimensions can increase with age
- Identification requires spectral domain optical coherence tomography in near-infrared reflectance modality

Lalvani S, et al. *J Multidiscip Healthc*. 2024;17:1803–1817. Kerashvili N, et al. *Expert Rev Neurother*. 2024;24:409–420.
Cosmo E, et al. *Cancers*. 2022;14:1423. Mallone F, et al. *Orphanet J Rare Dis*. 2022;17:223.

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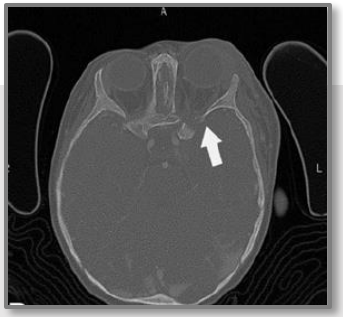
NF1
Additional Manifestations

Dermal Neurofibromas



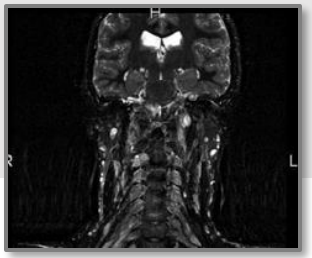
Dysplasia of Tibia and Sphenoid Bone





Cervical and Brachial PN





Optic Pathway Glioma



Korf BR. *Handb Clin Neurol*. 2013;111:333–340.
Gaillard F. Radiopaedia website. Updated April 3, 2025. https://radiopaedia.org/articles/optic-pathway-glioma.

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NF1
Diagnostic Criteria

1988

Diagnostic criteria for NF1 are met if **two or more** of the following are found:

1. Six or more café-au-lait spots (in the greatest diameter)
   - 1.5 cm or larger after puberty
   - 0.5 cm or larger before puberty
2. Freckling in the axilla or groin
3. Two or more Lisch nodules
4. Two or more neurofibromas OR one plexiform neurofibroma
5. Optic pathway glioma
6. A distinctive osseous lesion, such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis
7. First-degree relative with NF1

2021

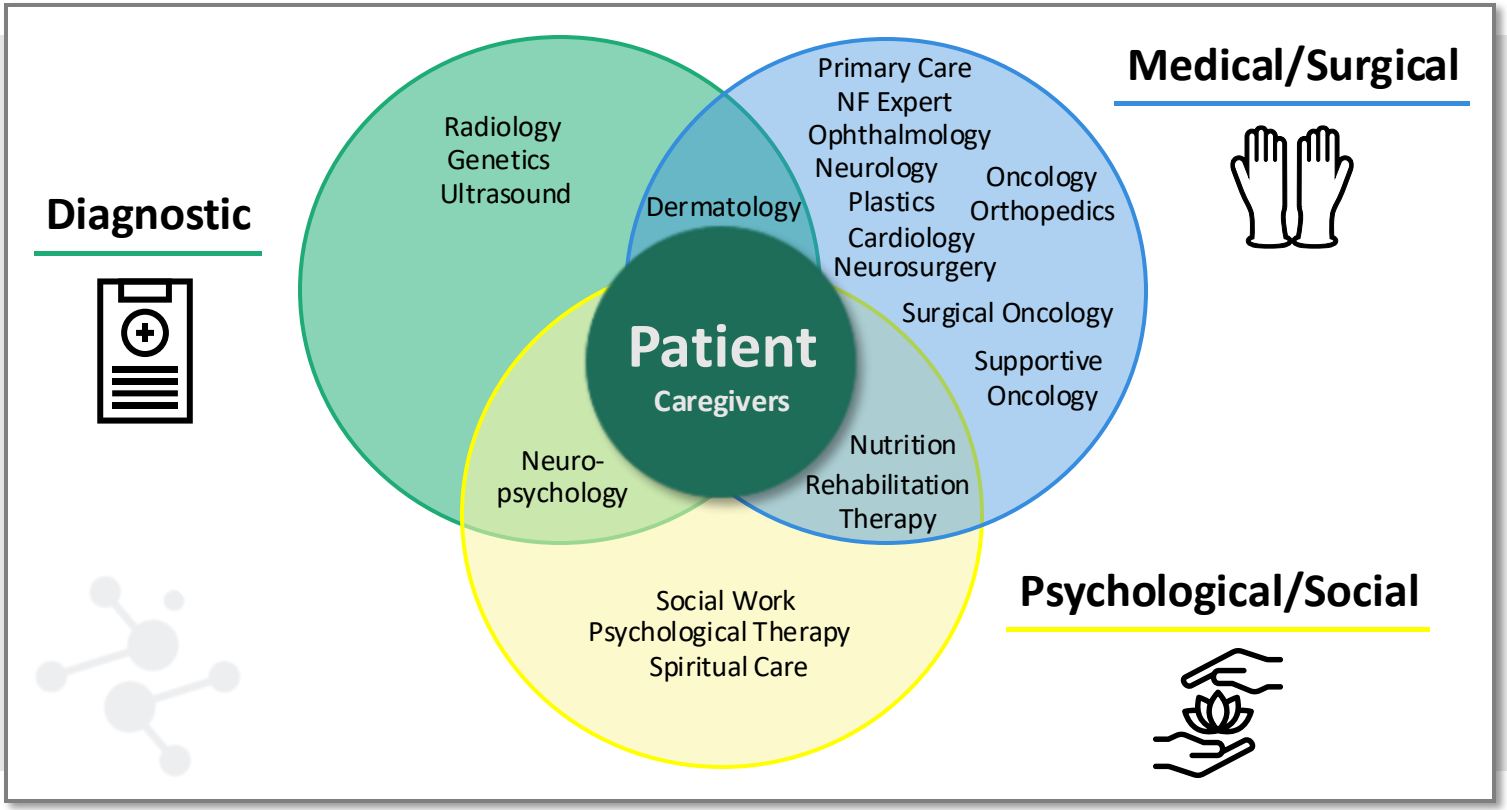
Diagnostic criteria for NF1 are met in an individual who **does not have a parent diagnosed with NF1** if **two or more** of the following are found:

1. Six or more café-au-lait spots (in the greatest diameter)
   - 1.5 cm or larger after puberty
   - 0.5 cm or larger before puberty
2. Freckling in the axilla or groin
3. Two or more neurofibromas OR one plexiform neurofibroma
4. Optic pathway glioma
5. Two or more iris Lisch nodules OR **two or more choroid abnormalities**
6. A distinctive osseous lesion, such as sphenoid dysplasia, anterolateral bowing of tibia or pseudoarthrosis of a long bone
7. **Heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue**

If a **parent meets the above diagnostic criteria**, the individual only requires one or more of the above criteria to merit an NF1 diagnosis

NIH Consensus Development Conference. *Neurofibromatosis.* 1988;1(3):172–178. Legius E, et al. *Genet Med.* 2021;23:1506–1513.

Multidisciplinary Care for Patients with NF1



Lalvani S, et al. *J Multidiscip Healthc*. 2024;17:1803–1817. Armstrong AE, et al. *BMC Cancer*. 2023;23(1):553.

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Role of Neurologist

- Contribute to diagnosis and initial evaluation of central and peripheral manifestations (e.g., neurocognitive impairment, weakness, signs of tumor growth [PNs, MPNSTs], optic pathway gliomas, seizure disorders, and cerebrovascular abnormalities)
- Monitor ongoing neurological symptoms (e.g., pain, weakness, numbness)
- Manage complications, such as seizures, headaches, and neuropathy
- Perform peripheral nerve ultrasound, electroencephalography, and electromyography/needle studies



Similar to primary care, neurologists frequently manage longitudinal care of patients with NF1

Lalvani S, et al. *J Multidiscip Healthc*. 2024;17:1803–1817.

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Irene (Renie) Moss



Renie Moss
Patient Advocate and Caregiver

Renie Moss lives in Alabama with her husband of 24 years, Philip Sr., and two children, Philip Jr. (age 20) and Helen (age 17), all three of whom have NF1. Ms. Moss is an avid advocate for the neurofibromatosis patient and research communities.

- Former chair of the Children's Tumor Foundation (CTF) Volunteer Leadership Council
- Former patient liaison to the Synodos NF1 Research Consortium
- Patient representative for Response Evaluation in Neurofibromatosis and Schwannomatosis International Collaboration (REiNS)
- Member of the University of Alabama–Birmingham (UAB) NF Clinic Patient Advisory Board
- Member of the UAB Genetic Counseling Program's advisory board

Renie Moss. Interview with CE Concepts. August 2025.

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Challenges of Accessing NF1 Care



Renie Moss

Patient Advocate and Caregiver



Renie Moss. Interview with CE Concepts. August 2025.

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Case: Angela T.



Angela T. is a 7-year-old female who has experienced some mild learning difficulties and clumsiness in school, which has been attributed to behavioral issues and not formally evaluated. She has a younger brother (4 years) and sister (2 years).

At her annual physical examination, her pediatrician notes axillary freckling and small, soft cutaneous nodules. Ophthalmologic exam finds Lisch nodules. NF1 is diagnosed based on clinical criteria. Parents do not have clinical characteristics of NF1.

Examination reveals:

- 9 café-au-lait spots >0.5 cm (largest 1.5 cm, multiple smaller spots), initially referred to as "birth marks" without follow up investigation
- Bilateral axillary freckling, no neurofibromas palpable
- Mild hypotonia, coordination difficulty noted
- No scoliosis on Adam's forward bend test; no long bone abnormalities
- Visual-spatial and processing deficits, attention and executive function concerns

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What do you recommend for this patient?

1. Continued typical pediatric care
2. Genetic evaluation
3. Neuropsychological testing
4. Occupational therapy
5. Referral to ophthalmology
6. Speech-language pathology testing
7. Magnetic resonance imaging (MRI) scans of brain/orbits
8. Recommend school support (Individualized Education Program [IEP] or 504 plan)
9. Monitoring blood pressure, head circumference
10. Baseline MRI imaging, cardiac and auditory assessments, bone density (x-ray lower extremities), electroencephalography (EEG)
11. Referral to comprehensive NF1 clinic

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Angela T. (…continued)



Recommendations

- Genetic testing for NF1 confirmation, at parents' request (concern for their other children)
- Comprehensive ophthalmologic exam
- Baseline neurological evaluation and developmental monitoring
- Refer to developmental-behavioral pediatrics for ADHD and behavioral support
- Genetic counseling to discuss inheritance, family testing, reproductive planning
- Continue occupational therapy and speech therapy per IEP
- Initiate parent support via Children's Tumor Foundation and/or local NF1 support networks
- Annual follow-up appointments for NF1 surveillance: neurological exam, skin, ophthalmology, growth and development

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Common Missed Opportunities

- Failure to recognize diagnostic criteria for NF1
- Underestimating the impact of mild developmental delays
- Delayed referral to specialists
- Inadequately taking family history
- Lack of coordination with schools
- Overlooking emotional and behavioral health
- Not referring to NF1 specialty clinics

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Difficulties in Diagnosis



Renie Moss

Patient Advocate and Caregiver



Renie Moss. Interview with CE Concepts. August 2025.

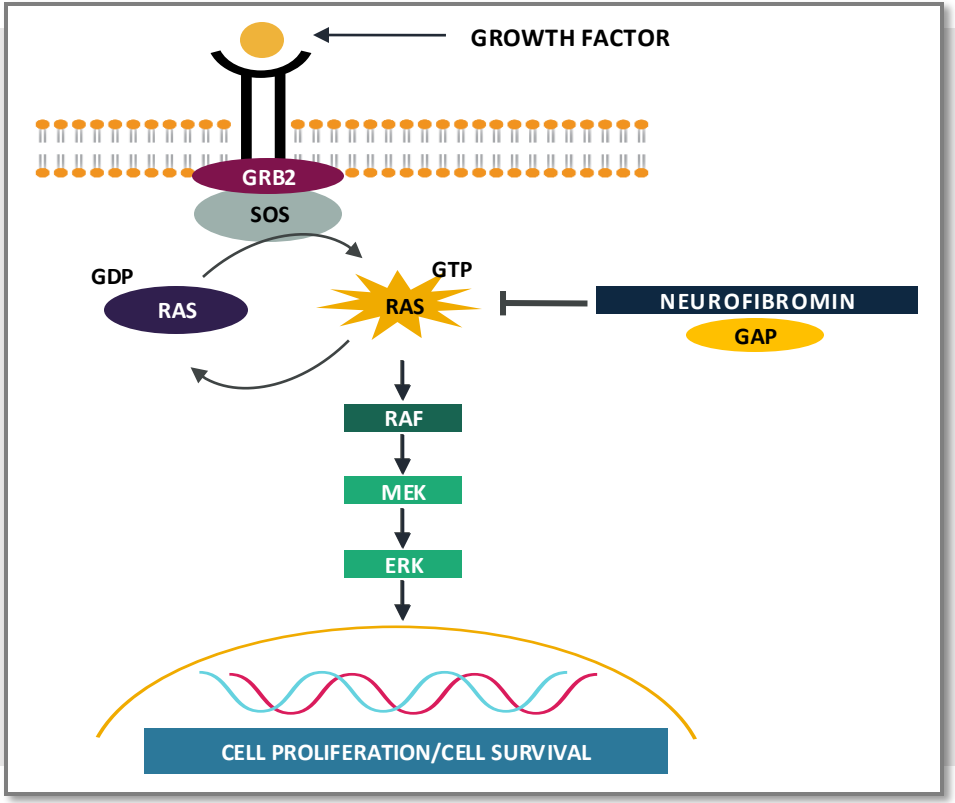
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Neurofibromatosis Type 1

MEK Inhibitors for the Treatment of Symptomatic, Inoperable Plexiform Neurofibromas in Children

Tumors Associated with NF1

- Dermal neurofibromas
- Plexiform neurofibromas (PNs)
- Optic pathway gliomas and other low-grade tumors
- Malignant peripheral nerve sheath tumors (MPNSTs)
- High-grade glioma
- Breast cancer
- Gastrointestinal stromal tumors (GISTs)
- Pheochromocytoma and/or paragangliomas
- Rhabdomyosarcomas



ERK, extracellular signal-regulated kinase; GAP, GTPase-activating proteins; GDP, guanosine diphosphate; GRB2, growth factor receptor-bound protein 2; GTP, guanosine triphosphate; MEK, mitogen-activated kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; SOS, Son of Sevenless.

Lalvani S, et al. *J Multidiscip Healthc*. 2024;17:1803–1817. Kerashvili N, et al. *Expert Rev Neurother*. 2024;24:409–420. Botero V, et al. *J Neurodev Disord*. 2024;16:49.

NF1-PNs

- Develop in up to 50% of patients with NF1
  - Typically, congenital or manifest in early childhood
  - Grow most rapidly in children <5 years of age
- Matrix of tumorigenic NF1-deficient Schwann cells, fibroblasts, endothelial cells, and mast cells
- Highly infiltrative, most frequently located in trunk or extremities
  - Multinodular enlargement
  - Can obstruct major organs, potentially life-threatening
    - Airway dysfunction, visual impairment, and bladder or bowel dysfunction
  - Pain, disfigurement, and motor dysfunction

Lalvani S, et al. *J Multidiscip Healthc*. 2024;17:1803–1817.
Acar S, er al. *Expert Opin Investig Drugs*. 2022;31:31–40. Kerashvili N, et al. *Expert Rev Neurother*. 2024;24:409–420.

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NF1-PNs

- Most patients have ≥1 PN-associated morbidity
  - Most common: pain, disfigurement, and motor dysfunction
  - Other comorbidities of note: defects in vision, airway, and bowel/bladder function
  - Morbidities tend to worsen over time without treatment
- Symptomatic PNs tend to be larger than asymptomatic PNs
  - Asymptomatic and symptomatic often coexist
- Benign, but may progress to atypical neurofibromas and then undergo transformation to MPNST
  - Estimated lifetime risk of MPNST in patients with NF1 is 8%–13%
  - Risk of transformation to MPNST is higher in patients with NF1

Lalvani S, et al. *J Multidiscip Healthc*. 2024;17:1803–1817. Armstrong AE, et al. *BMC Cancer*. 2023;23(1):553.
Acar S, er al. *Expert Opin Investig Drugs.* 2022;31:31–40. Kerashvili N, et al. *Expert Rev Neurother*. 2024;24:409–420.

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NF1-PN Management
Observation vs Treatment

INTERTWINED CONSIDERATIONS
- Age of patient
- PN growth status
- Growth rate
- Present/impending morbidity
- Progressive nature of tumor

OBSERVATION
- Not all patients with NF1-PN require treatment
- Most stable tumors do not cause morbidity
- May not progress or cause symptoms
- Management involves regular monitoring

TREATMENT
- Goal (most cases) to improve or prevent PN-associated morbidity
- Consider when evidence shows/ suggests PN-related morbidity or tumor growth with impending morbidity

Lalvani S, et al. *J Multidiscip Healthc.* 2024;17:1803–1817.
Armstrong AE, et al. *BMC Cancer*. 2023;23(1):553. Fischer MJ, et al. *Neuro Oncol*. 2022;24:1827–1844.

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NF1-PN Management
Surgery vs Medical Treatment

PRIOR TO TREATMENT

- Rule out malignant transformation of PN
- Assess change in tumor growth rate (i.e., new onset or recent change in PN-related pain)
- Biopsy if clinical concern
- Multidisciplinary input needed
- Note
  - Medical therapy for NF1-PN does not prevent transformation to MPNST
  - Treatment is different for MPNST vs NF1-PN

SURGERY

- Preferred if resection can be achieved without significant morbidity
- Complete tumor excision: ~15% of cases
- NF1-PN regrowth (post partial or subtotal resection): ~43%
- Permanent sequelae (neurologic): 5%–18% of patients

MEDICAL TREATMENT

- Preferred if specific contraindications or pre-existing conditions
- Concerns related to a therapeutic option
- Assess logistics, adverse events, formulation, compliance, long-term safety, etc.

Lalvani S, et al. *J Multidiscip Healthc.* 2024;17:1803–1817.
Armstrong AE, et al. *BMC Cancer*. 2023;23(1):553. Fischer MJ, et al. *Neuro Oncol.* 2022;24:1827–1844.

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Angela T. (…continued)



At 10 years of age, she develops a slowly enlarging, diffuse swelling along the lower left jaw and neck. This area feels rubbery, is sometimes tender, and grows steadily but unpredictably. The mass is non-resectable due to its size and location and causes cosmetic deformity and periodic discomfort. MRI confirms a plexiform neurofibroma.

Over several years, the lesion causes noticeable facial asymmetry and mild difficulty with chewing and speech. She begins to experience neuropathic pain and occasional airway discomfort by age 13–14. Function and quality of life (QoL) decline, and the mass becomes increasingly prominent.



At 15 years of age, progressive pain, impaired function, and disfigurement are negatively impacting her QoL.

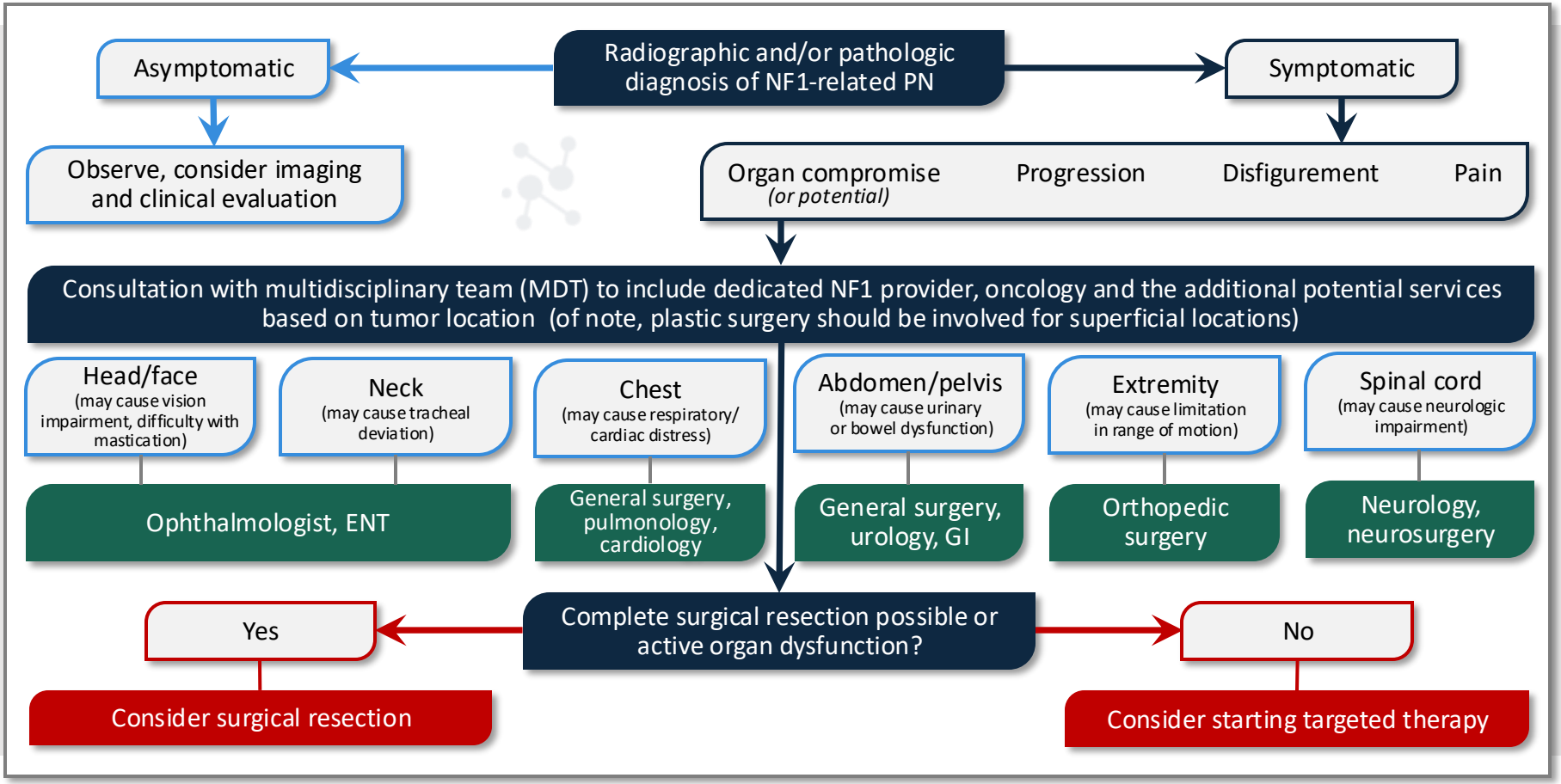
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Which do you recommend for this patient?

A. Continued observation
B. Multidisciplinary tumor board
C. Surgery
D. Radiation therapy
E. Systemic therapy

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Multidisciplinary Team Management Algorithm for NF1-PN



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

Recommendations

- Complete resection is not possible
- In consultation with her parents, it is decided that she receive systemic therapy

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Targeted Medical Therapy for NF1-PN

Several MEK inhibitors and tyrosine kinase inhibitors (TKIs) have demonstrated activity against NF1-PN.

Outcomes of note in clinical trials:

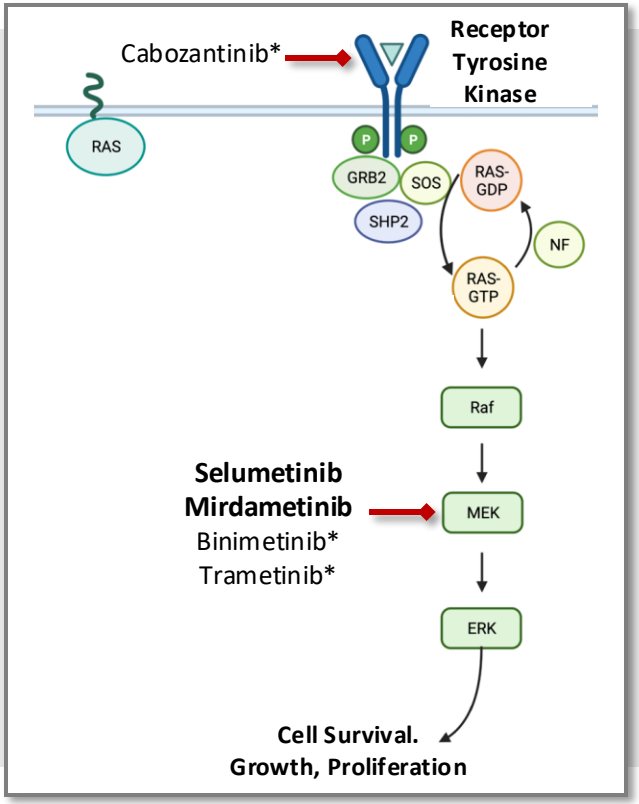
- Assessed PN growth and response via 3D volumetric analysis
- Patient-reported and functional outcome assessments

SELUMETINIB

FDA-approved in *pediatric* patients **1 year of age and older** with NF1 who have symptomatic, inoperable PN

MIRDAMETINIB

FDA-approved in *adult and pediatric* patients 2 years of age and older with NF1 who have symptomatic PN not amenable to complete resection

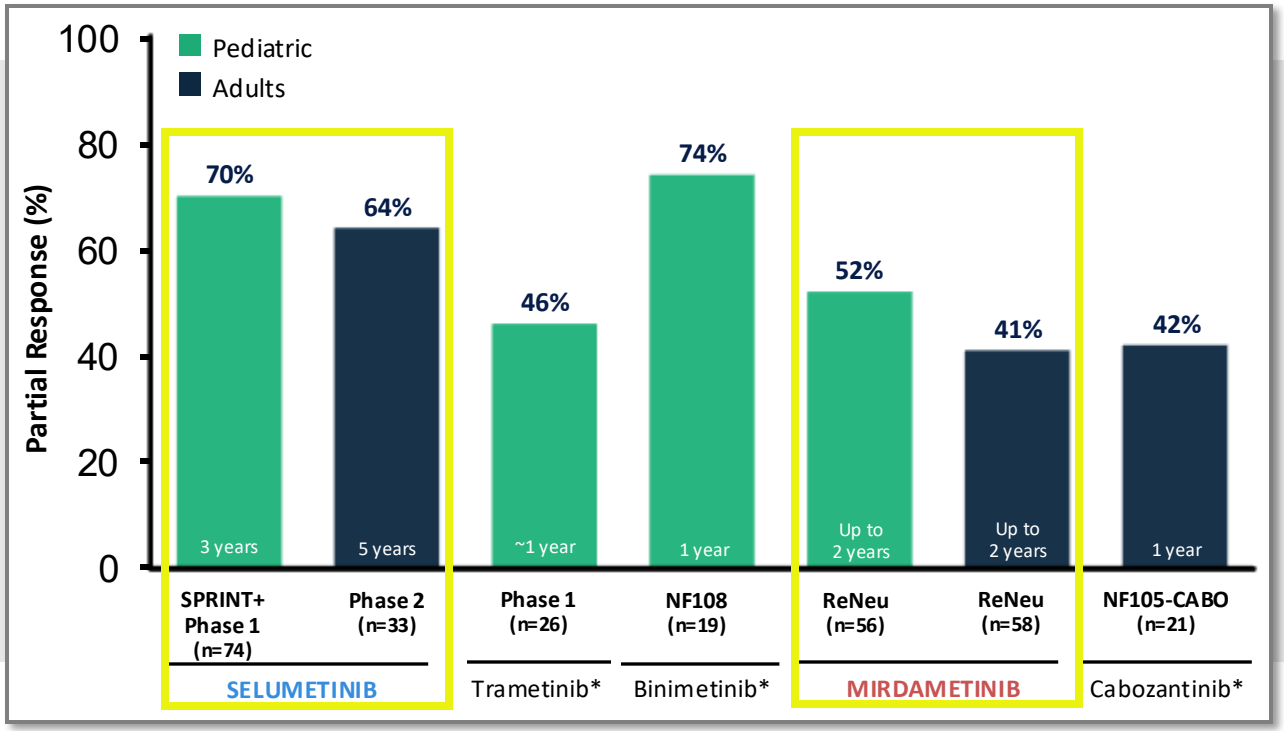


*Not FDA approved for the treatment of NF1-PN.

NF, neurofibromin; SHP2, Src homology-2 protein tyrosine phosphatase.

Na B, et al. *Curr Oncol Rep*. 2024;26:706–713. Armstrong AE, et al. *BMC Cancer*. 2023;23(1):553.
Fischer MJ, et al. *Neuro Oncol*. 2022;24:1827–1844. de Blank PM, et al. *Neuro Oncol*. 2022;24:1845–1856.
Mirdametinib (package insert). Revised February 2025.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219379Orig1s000lbl.pdf.
FDA. FDA website. Press release September 10, 2025.
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selumetinib-pediatric-patients-1-year-age-and-older-neurofibromatosis-type-1

Overview of Reported Partial Response Rates with MEKis and Cabozantinib in NF1-PN



Efficacy Snapshot

- Overall response rates
  - 41%–74%
- Median time to response
  - Cycles 5 and 12
- Maximum response
  - Cycles 15 and 20
- Outcomes not reached
  - Median DoR
  - Median PFS

Cross-trial comparisons are not valid

*Binimetinib, cabozantinib, and trametinib are not FDA approved for the treatment of NF1-PN.
DoR, duration of response; PFS, progression-free survival.

Gross AM, et al. *Nat Med*. 2025;31(1):105–115. Solares I, et al. *ESMO Open*. 2021;6(4):100223.
Gross AM, et al. *Neuro Oncol*. 2023;25:1883–1894. Moertel CL, et al. *J Clin Oncol*. 2025;43(6):716–729.

SPRINT Trial

Selumetinib in Children with Inoperable PN

- Phase 2, open-label
- Children (2–18 years of age)
- NF1 + symptomatic inoperable PN
- No evidence of MPNST, an optic glioma, malignant glioma, or other cancer requiring treatment with chemotherapy or radiation therapy

Baseline Demographics (median values)

- Age: 10 years
- Male: 60%
- Volume of target NF: 487 mL
- Progression status (progressive/not/data lacking): 42%/30%/28%
- Location of target NF
  - Neck + trunk (24%), trunk + limbs (24%), head (18%), head + neck (16%), trunk (10%), limbs (8%)
- NF-related comorbidities (median number: 3)
  - Disfigurement (88%), motor dysfunction (66%), pain (52%), airway (32%), vision (20%), bowel or bladder (20%), other (22%)

Selumetinib 25 mg/m^2 BSA BID (n=50)
Treatment cycle: 28 days (no rest between cycles)

Up to 2 years if no drug-related toxicity or progressive disease
(≥20% volume increase in target PN)



Primary Endpoint

- Partial response (≥20% volume reduction in target PN by 3D analysis of MRI)
  - Confirmed (2 consecutive)
  - Durable (lasting ≥12 cycles)

Secondary Endpoints

- Duration of response
- Safety
- Patient-observer reported outcomes

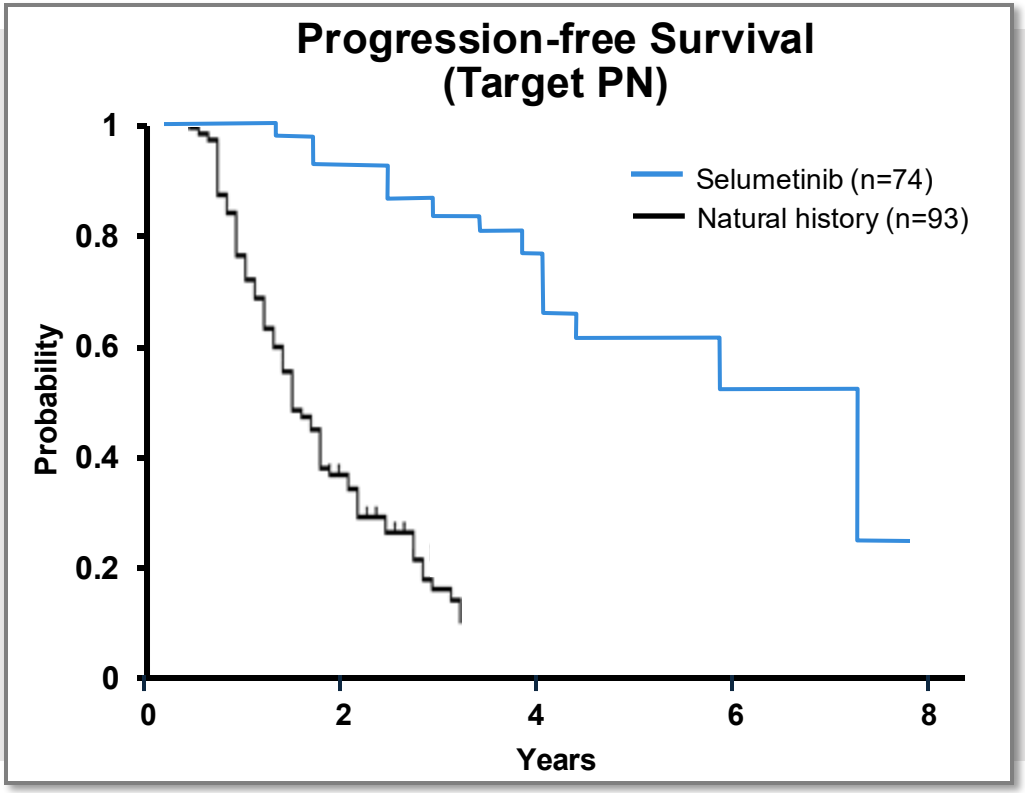
BID, twice daily; BSA, body surface area.

Gross AM, et al. *N Engl J Med*. 2020;382:1430–1442.

Combined 5-year Progression-Free Survival

SPRINT + Phase I

- Combined cohort (n=74)
  - Continuous selumetinib dosing (median duration: 57.5 cycles)
  - Remaining on treatment at data cutoff (n=31)
- Partial response
  - Confirmed and durable: 70% and 59%
- Time to response (median)
  - Initial: 8 cycles (range 4–40)
  - Best response: 18 cycles (range 4–94)
- Median PFS
  - 88 cycles (7.3 years)
- 1-year probability of being progression-free after
  - 60 cycles: 61% (95% CI, 46–73)



Gross AM, et al. *Neuro Oncol*. 2023;25:1883–1894.

Selumetinib Adverse Events

All grade (Grade 3–4)	Gastrointestinal	Skin and Subcutaneous Tissue	Other Toxicities
≥80%	Vomiting (6%)	All rashes* (6%)	
50%–79%	Abdominal pain Diarrhea (16%) Nausea (2%) Stomatitis	Dry skin Rash acneiform (4%)	Increased CPK (7%) Musculoskeletal pain Fatigue Pyrexia (8%)
20%–49%	Constipation	Paronychia (6%) Pruritus Dermatitis (4%) Hair changes	Headache (2%) Epistaxis Hematuria (2%) Proteinuria Decreased appetite Decreased ejection fraction Sinus tachycardia Skin infection (2%) Edema

Adverse events (AEs) occurring in ≥20% of patients.
*Rash (all) includes dermatitis acneiform, rash maculo-papular, erythema, rash pustular, rash, urticaria, exfoliative rash, rash pruritic, and rash erythematous.
CPK, creatine phosphokinase.

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Selumetinib (package insert). Revised January 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213756s004lbl.pdf.

Selumetinib AEs of Special Interest

Ocular			
Adverse Event, n	**Grade 1**	**Grade 2**	**Grade 3**
Blurred vision	4	0	0
Cataract	1	0	0
Dry eye	1	1	0
Eye disorders (other)	2	0	0
Eye pain	1	0	0
Photophobia	1	0	0
Photosensitivity	2	1	0
Retinopathy	1	0	0
Watering eyes	1	0	0

Cardiac			
Adverse Event, n	**Grade 1**	**Grade 2**	**Grade 3**
Ejection fraction decreased	0	14	1
Hypertension	6	2	0
Sinus bradycardia	2	0	0
Sinus tachycardia	2	0	0

Safety population, N=74

No grade 4 ophthalmological or cardiac AEs reported

Gross AM, et al. *Neuro Oncol*. 2023;25:1883–1894.

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Selumetinib*

Warnings and Precautions

- Ocular toxicity: blurred vision, photophobia, cataracts, and ocular hypertension
  - 15% of pediatric population (resolved in 82%)
- Cardiomyopathy
  - Decreased LVEF of ≥10% occurred in 23% of pediatric patients (all were identified during routine echocardiography); decreased LVEF resolved in 71% of these patients
- Skin toxicity
  - Rash occurred in 91% of pediatric patients (8% Grade 3); the most frequent rashes included dermatitis acneiform (54%), maculopapular rash (39%), and eczema (28%)
- Gastrointestinal toxicity
  - Diarrhea in 77% of pediatric population (15% Grade 3)
- Increased creatine phosphokinase
  - Occurred in 76% of pediatric population (9% Grade 3 or 4)
- Risk of bleeding
  - Vitamin E is excipient and can inhibit platelet aggregation and antagonize vitamin K-dependent clotting factors
- Embryo-fetal toxicity

Toxicities seen in an unapproved adult population* with multiple tumor types who received selumetinib as a single agent or in combination with other anti-cancer agents:

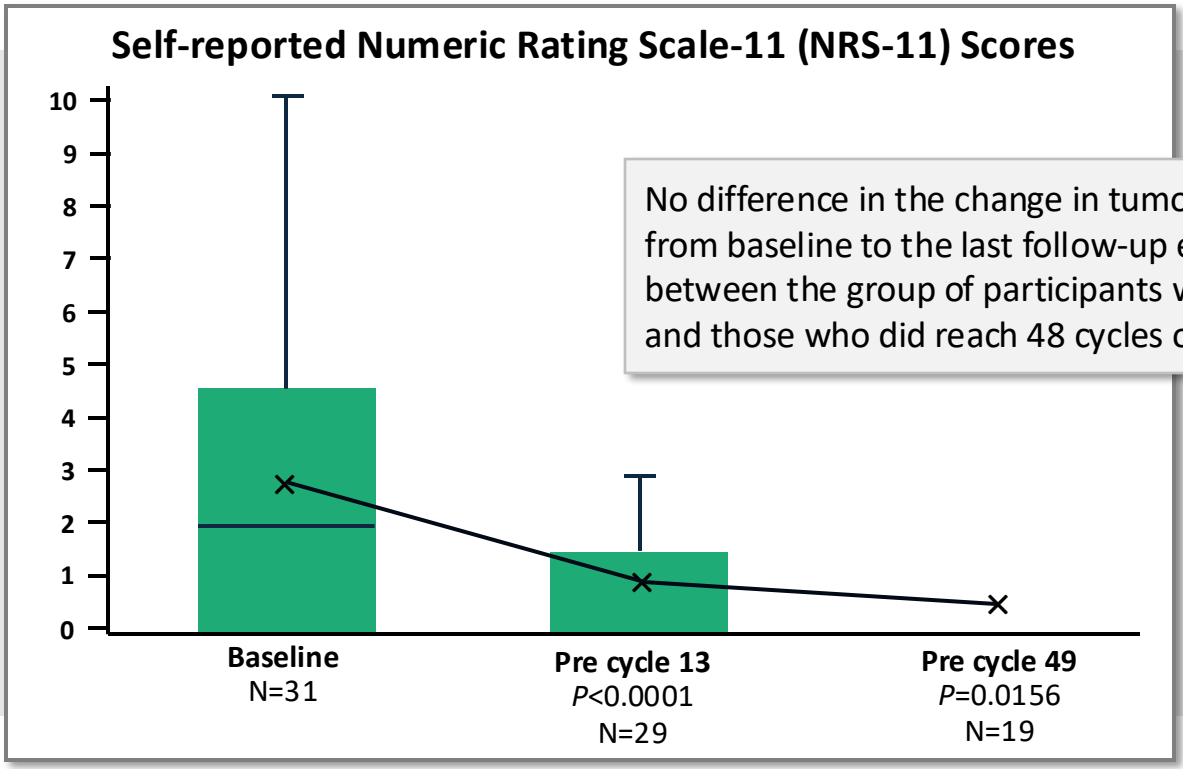
- Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED)
- Intestinal perforation, colitis, ileus, and obstruction
- Cardiomyopathy (decreased left ventricular ejection fraction [LVEF])
- Severe palmar-plantar erythrodysesthesia syndrome
- Rhabdomyolysis

*Selumetinib is not FDA approved in adult patients who have a PN.

Selumetinib (package insert). Revised January 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213756s004lbl.pdf.

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Selumetinib
Patient-Reported Pain



Gross AM, et al. *Neuro Oncol*. 2023;25:1883–1894.

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ReNeu Trial

Mirdametinib in Children and Adults with Inoperable PN

- Phase 2, open-label
- Age-based cohorts
  - Pediatric (2–17 years)
  - Adults (≥18 years)
- NF1 + inoperable progressive and/or symptomatic PN

Baseline Demographics (pediatric [n=56]/adults [n=58])

- Median age: 10/58 years
- Male: 46%/36%
- Location of NF
  - Head + neck (50%/48%), lower-upper extremities (14%/29%), paraspinal (7%/9%), other (29%/14%)
- NF-related complications
  - Pain (70%/90%), disfigurement-major deformity (50%/52%), motor dysfunction or weakness (27%/40%), airway dysfunction (13%/5%), other (21%/17%)
- Target PN progressing: 63%/53%

Mirdametinib 2 mg/m² BID (max 4 mg/m²)

Treatment cycle: 28 days (3 weeks on, 1 week off)

Up to 2 years

Primary Endpoint

- Partial response (≥20% volume reduction in target PN by volumetric MRI)

Secondary Endpoints

- Duration of response
- Safety
- QoL and physical functioning

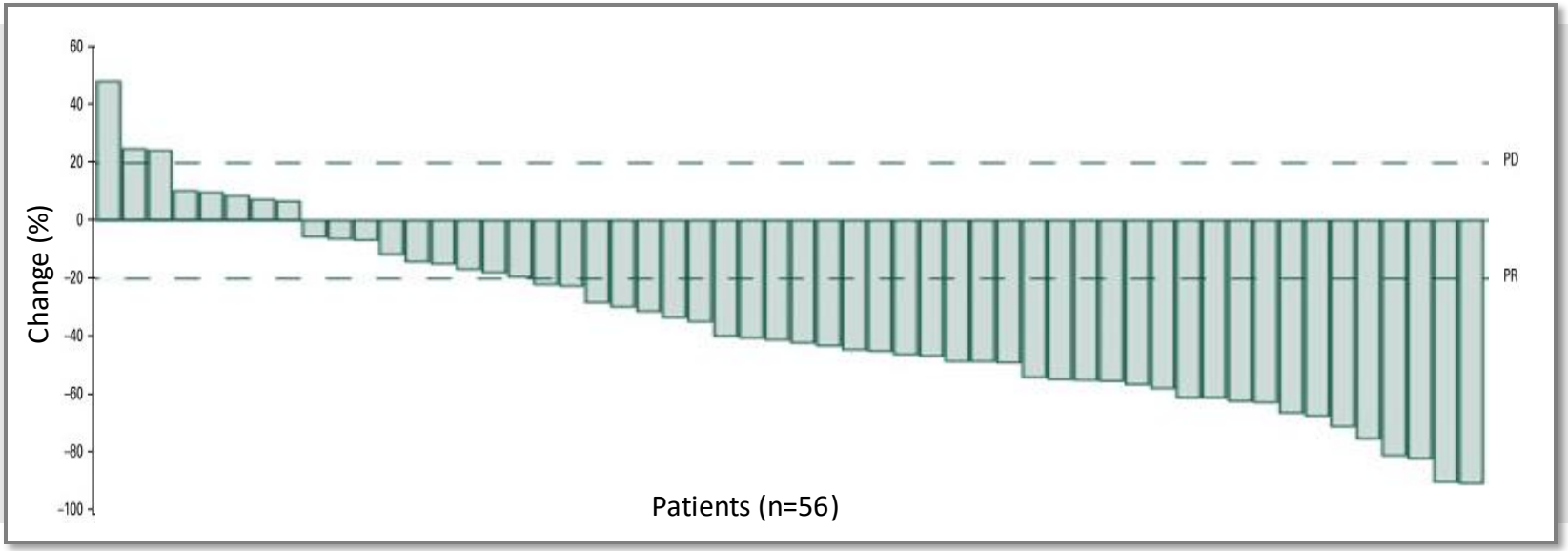
Moertel CL, et al. *J Clin Oncol*. 2025;43(6):716–729.

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ReNeu (Pediatrics)

Best Change from Baseline in Target PN Volume per Patient

Best Percent Change in Target PN Volume



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

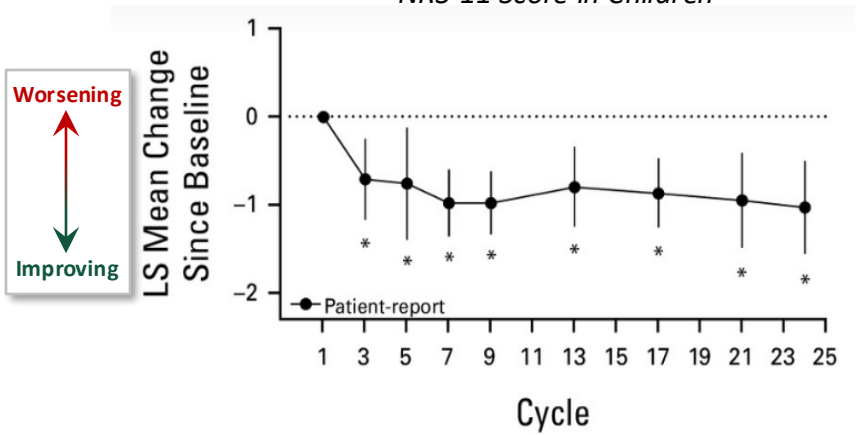
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ReNeu (Pediatrics)

Pain and QoL

Patient-reported Pain

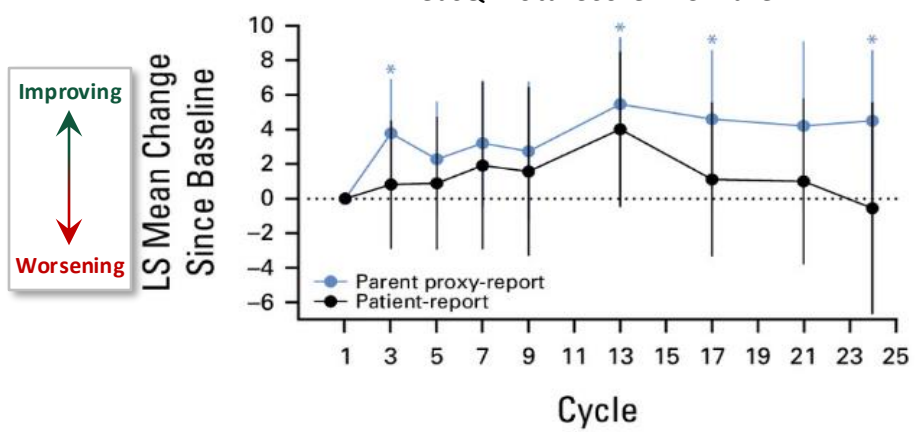
NRS-11 Score in Children



No. patients									
Patient-report	36	23	25	24	23	17	18	11	8

Patient-reported QoL

PedsQL Total Score in Children



No. patients									
Patient-report	50	48	47	41	42	38	34	32	29
Parent proxy-report	55	52	52	48	47	43	36	36	33

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

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ReNeu Adverse Events (Pediatrics)

All grade (grade 3–4)	Skin and Gastrointestinal	Other Toxicities
≥80%		
50%–79%	Rash* (4%) Diarrhea (5%)	Increased CPK (5%)
20%–49%	Nausea Vomiting Abdominal pain (4%) Stomatitis	Musculoskeletal pain (2%) Headache (2%) Paronychia Left ventricular dysfunction (2%) Increased triglycerides, creatinine, alk-phos, ALT COVID-19 Upper respiratory tract infection Decreased glucose, calcium, bicarbonate Cough Pyrexia Decreased hemoglobin, leukocytes, neutrophils, lymphocytes Increased lymphocytes

alk-phos, alkaline phosphatase; ALT, alanine aminotransferase.
AEs occurring in ≥20% of patients; data for adult patients is not included.
*Rash includes dermatitis acneiform, eczema, maculo-papular rash, pustular rash, dermatitis, erythematous rash, palmar-plantar erythrodysesthesia syndrome, exfoliative rash, skin exfoliation, pruritic rash, papule, papular rash, and macular rash.

Mirdametinib
Warnings and Precautions

- Ocular toxicity: retinal vein occlusion (RVO), retinal pigment epithelium detachment (RPED), and blurred vision
  - Occurred in 25% of patients; 20% Grade 1, 3.8% Grade 2, and 0.8% Grade 3
- Left ventricular dysfunction
  - Decreased LVEF of 10%–<20% occurred in 20%, and decreased LVEF of ≥20% occurred in 0.9% of patients (all were identified during routine echocardiography); decreased LVEF resolved in 75% of these patients
- Dermatological AEs
  - Rash occurred in 84% of patients (31% Grade 2; 6% Grade 3); the most frequent rashes (≥2%) included dermatitis acneiform (65%), rash (11%), eczema (8%), maculo-papular rash (4.5%) and pustular rash (3.8%)
- Embryo-fetal toxicity

Mirdametinib (package insert). Revised February 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219379Orig1s000lbl.pdf.

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Angela T. (…continued)



Angela is now 19 years old and has been receiving selumetinib continuously for symptomatic PN. The tumor shrank and is now stable. Her pain also improved. However, the indication for selumetinib is for "pediatric patients 1 year of age and older."

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What would you do?

A. Stop therapy
B. Switch to mirdametinib
C. Stay on selumetinib

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Neurofibromatosis Type 1

Transition of Care

The Role of Peers in the Transition from Pediatric to Adult Care



Renie Moss

Patient Advocate and Caregiver

Clinical Perspective
Transition from Pediatric to Adult Care

- Developmental delays
- Scholastic concerns
- Plexiform neurofibromas
- Autism/ADD
- Optic pathway gliomas
- Bone abnormalities

- Dermal neurofibromas
- Malignant progression
- Pain
- Glioblastoma
- Breast cancer
- Family planning

Birth → **18 years** → **Adult**

Multidisciplinary Care

- Neurology
- Medical oncology
- Orthopedics
- Neurosurgery
- Plastic surgery
- Dermatology
- Psychiatry
- PT/OT

The transition of care is a process of moving from pediatric-centered to adult-centered care with or without transition to a new clinician.

ADD, attention deficit disorder; OT, occupational therapy; PT, physical therapy.
*Based on Dr. Angela Hirbe's clinical experience and opinion.

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Transition from Pediatric to Adult Care

Differences in Delivery of Care

	Pediatric Care Model	Adult Care Model
Practice approach	• Family-centered • Shared decision-making with parents	• Patient-centered • Shared decision-making with patient
Multidisciplinary staffing	• Multiple subspecialists are often available for an MDT approach to care—"one-stop shop"	• Few or no "one-stop shop" multidisciplinary clinics • Separate referrals/appointments for each specialist needed
Coordination of care and access to support services	• Coordination of care often provided by clinic coordinator or nurse navigator • Social work and case management support is often available	• Care coordination services are not often provided; few public care coordination programs are available for adults with NF1 • Less social work, case management staffing, and support available
Length of appointment	• Long	• Short
Adherence to care	• Frequent reminders and support from healthcare system • Healthcare provider has the duty to report non-adherence that may reach a level that looks like medical negligence	• Expectation of self-adherence; often no appointment reminders or follow-up from missed appointments • Healthcare provider has no reporting duty of non-adherence, unless patient has a court-appointed guardian and is being neglected per provider opinion

MDT, multidisciplinary team.

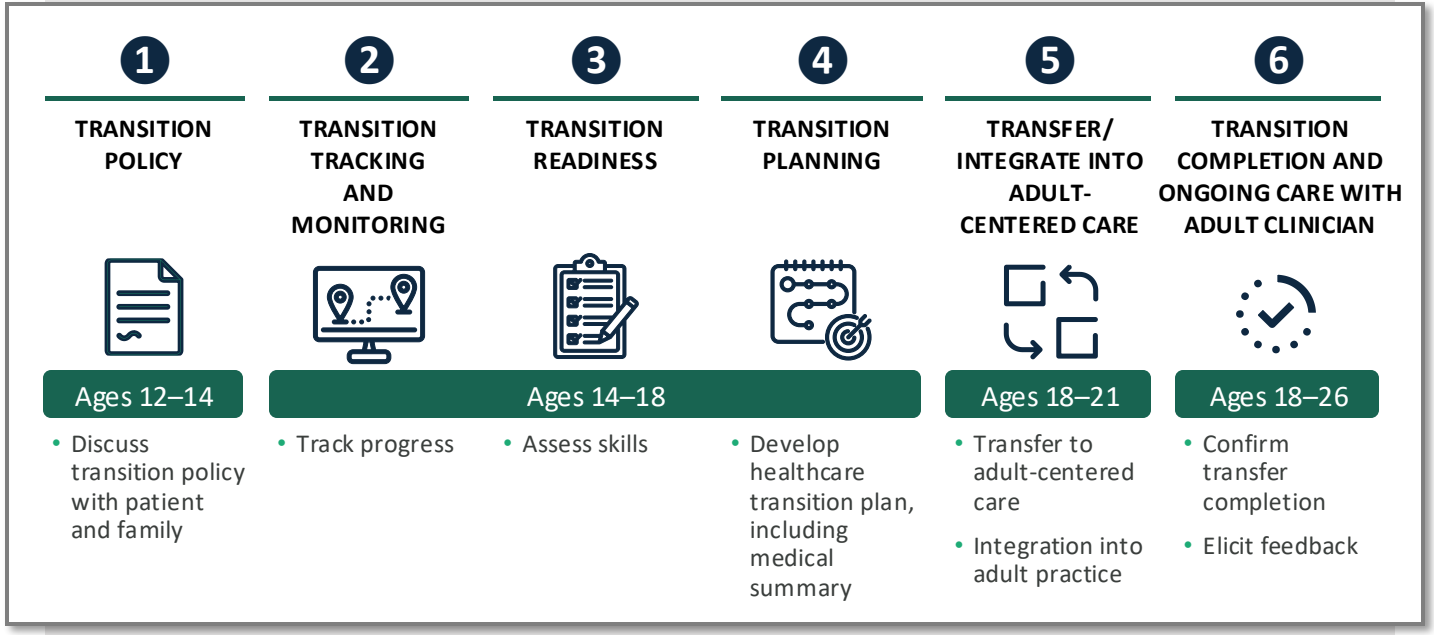
White PH, et al. *Pediatrics*. 2018;142:e20182587. Radtke HB, et al. *Pediatric Health Med Ther*. 2023;14:19–32.

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Core Elements of Health Care Transition

Key Elements for Transition to Adulthood Program

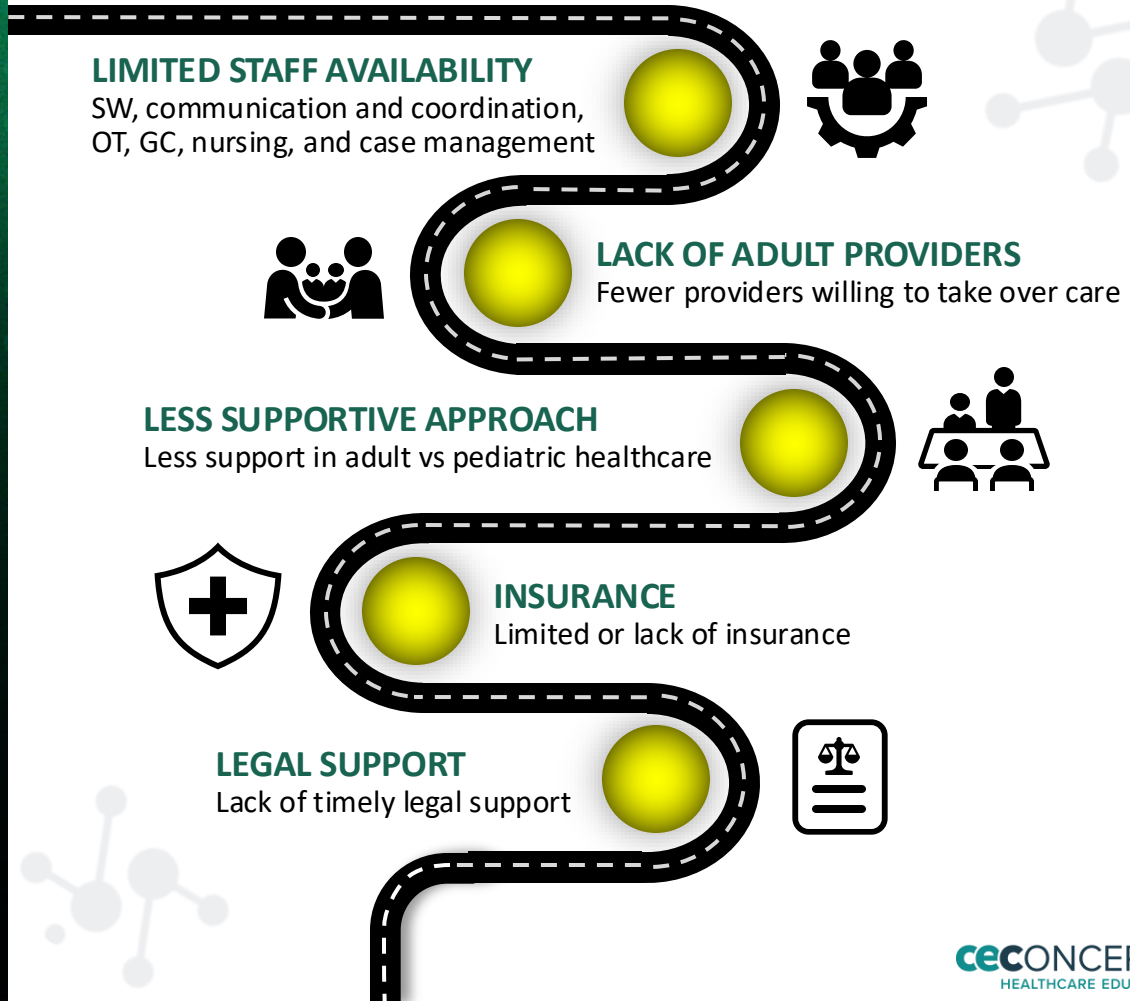
- Annual assessments to plan transition
- Establishment of yearly personal goals
- Bi-monthly adolescent and young adult transition planning meetings
- Dedicated collaborative specialists across the lifespan



White PH, et al. *Pediatrics*. 2018;142:e20182587. Radtke HB, et al. *Pediatric Health Med Ther*. 2023;14:19–32.

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BARRIERS to Successful NF1 Health Care Transitions

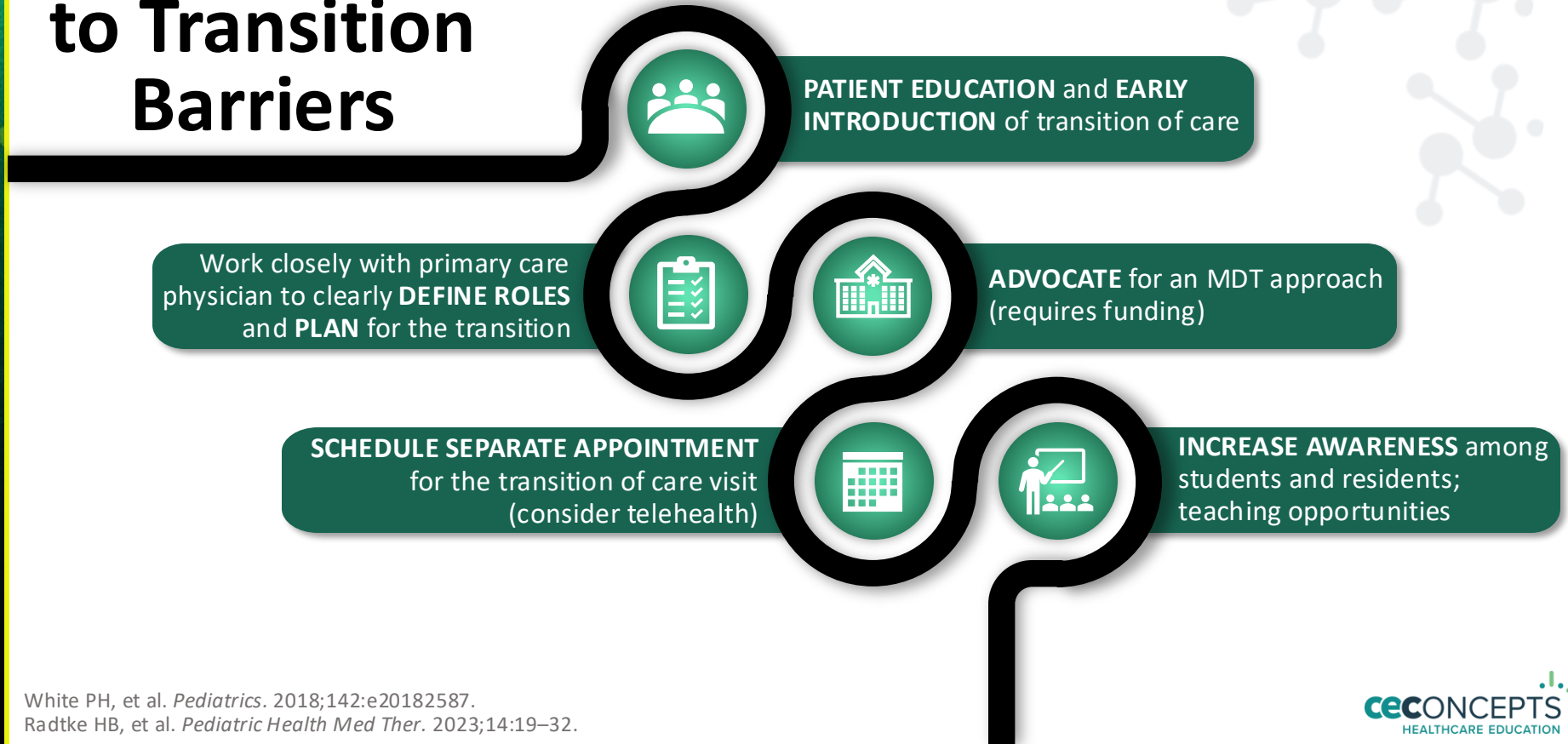


GC, genetic counselling; SW, social work.

White PH, et al. Pediatrics. 2018;142:e20182587.
Radtke HB, et al. Pediatric Health Med Ther. 2023;14:19–32.

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Potential SOLUTIONS to Transition Barriers



White PH, et al. *Pediatrics*. 2018;142:e20182587.
Radtke HB, et al. *Pediatric Health Med Ther*. 2023;14:19–32.

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Tools to Aid Transition of Care

GOT TRANSITION is a national resource center on health care transition in the United States. Its aim is to “improve transition from pediatric to adult health care through the use of evidence-driven strategies for health care professionals, youth, young adults, and their families.”



Got Transition website. 2025. https://www.gottransition.org/.

Long-Term Planning



Renie Moss

Patient Advocate and Caregiver

Optimizing Transitioning Children to Adult Care

- Decreased transition readiness in NF1 is associated with a negative impact in adult life
- Challenges associated with the transition of care in NF1 need to be recognized
- Key aspects to consider when planning for transition of care in NF1 include
  - Identification of adult providers
  - Establishing and monitoring readiness over time
  - Updating medical records and transition plan
  - Health insurance
- There are tools and resources available to help manage NF1 care and achieve a successful transition of care
  - Got Transition: https://www.gottransition.org/
  - Children's Tumor Foundation: https://www.ctf.org/

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Neurofibromatosis Type 1

MEK Inhibitors for the Treatment of Symptomatic, Inoperable Plexiform Neurofibromas in Adults

Case: Mary G.



Mary G. is a 45-year-old female with a painful facial PN that is also causing significant deformity. The pain is similar to what it has been for years (i.e., no new/changing pain). Her MRI does not demonstrate concerning features of the tumor.

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What is the next best step?

A. Biopsy
B. Start MEKi after MDT discussion
C. Surgery

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ReNeu Trial

Mirdametinib in Children and Adults with Inoperable PN

- Phase 2, open-label
- Age-based cohorts
  - Pediatric (2–17 years)
  - Adults (≥18 years)
- NF1 + inoperable progressive and/or symptomatic PN

Baseline Demographics (pediatric [n=56]/adults [n=58])

- Median age: 10/58 years
- Male: 46%/36%
- Location of NF
  - Head + neck (50%/48%), lower-upper extremities (14%/29%), paraspinal (7%/9%), other (29%/14%)
- NF-related complications
  - Pain (70%/90%), disfigurement-major deformity (50%/52%), motor dysfunction or weakness (27%/40%), airway dysfunction (13%/5%), other (21%/17%)
- Target PN progressing: 63%/53%

Mirdametinib 2 mg/m² BID (max 4 mg/m²)

Treatment cycle: 28 days (3 weeks on, 1 week off)

Up to 2 years

Primary Endpoint

- Partial response (≥20% volume reduction in target PN by volumetric MRI)

Secondary Endpoints

- Duration of response
- Safety
- QoL and physical functioning

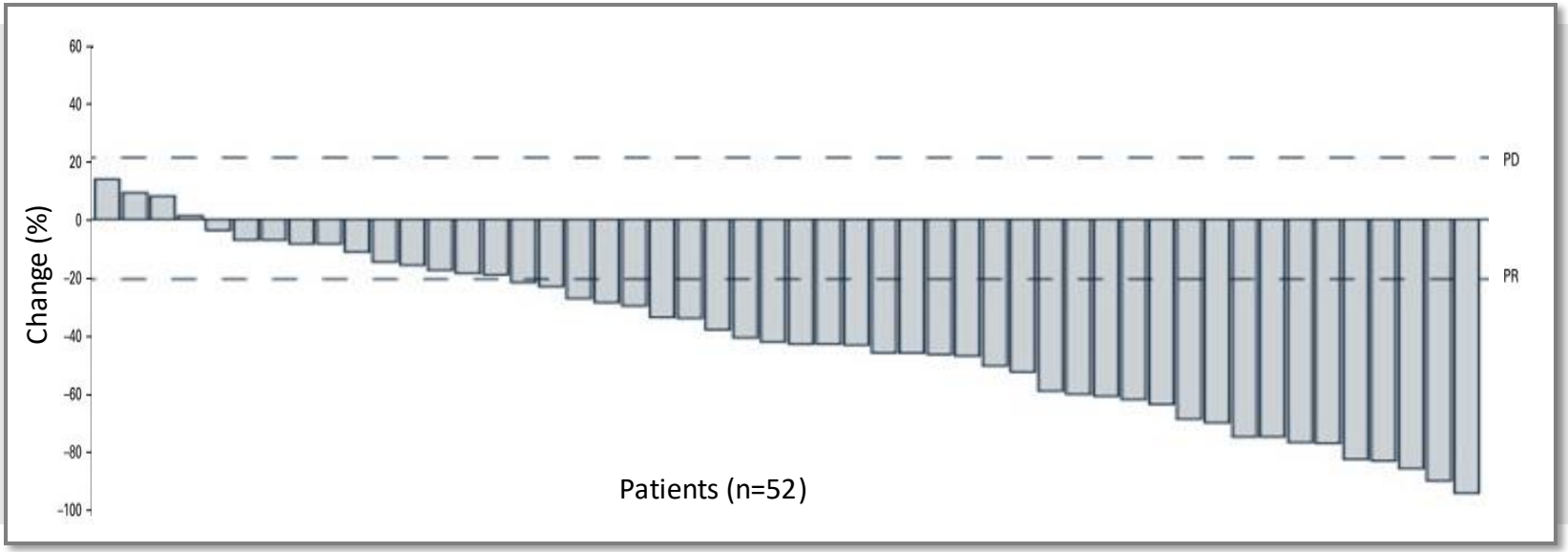
Moertel CL, et al. *J Clin Oncol*. 2025;43(6):716–729.

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ReNeu (Adult)

Best Change from Baseline in Target PN Volume per Patient

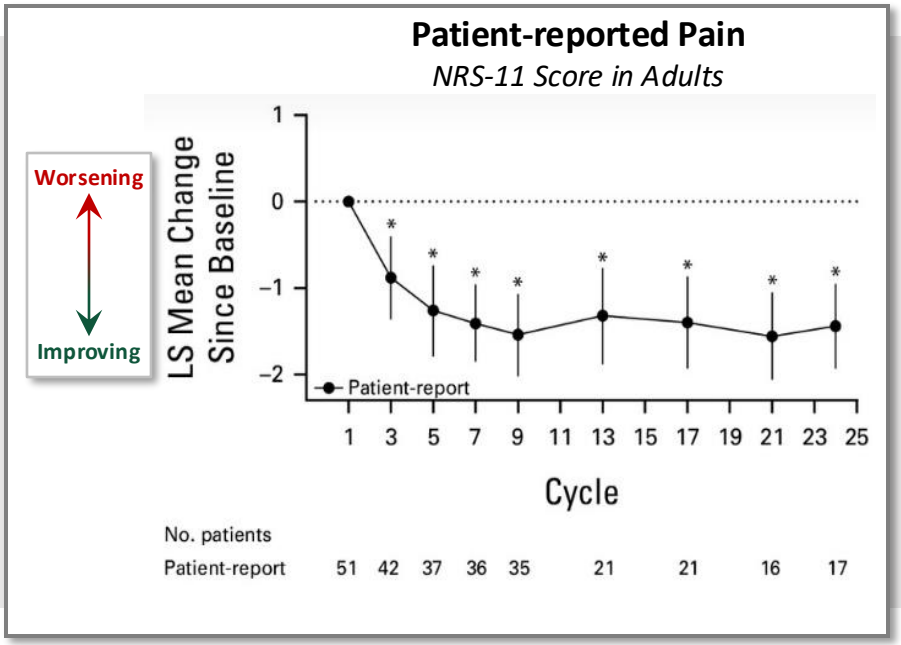
Best Percent Change in Target PN Volume

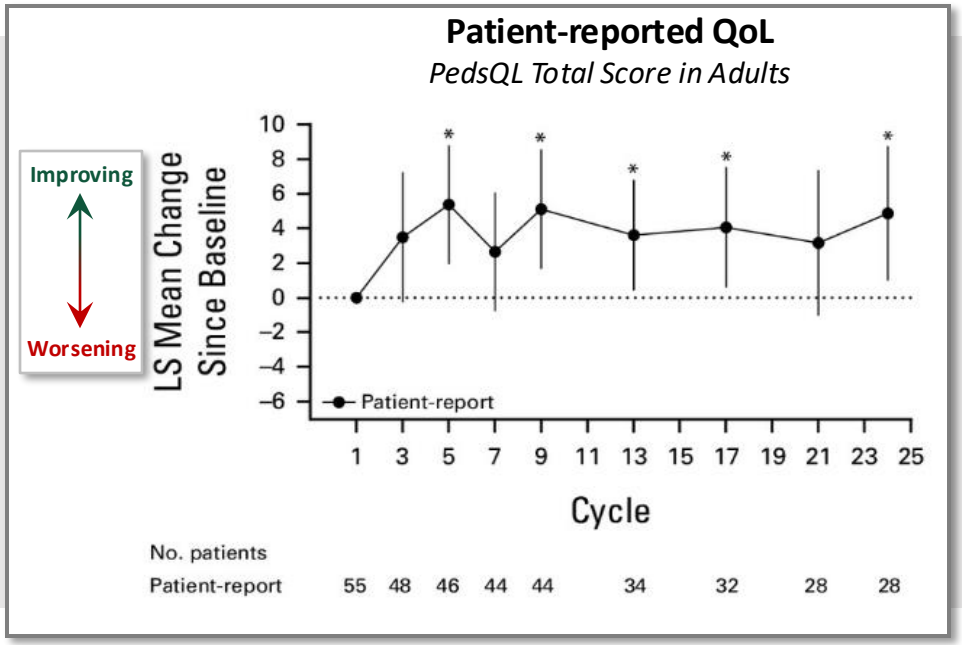


Moertel CL, et al. *J Clin Oncol*. 2025;43(6):716–729.

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ReNeu (Adult)
Pain and QoL





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

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ReNeu Adverse Events (Adult)

All grade (grade 3–4)	Skin and Gastrointestinal	Other Toxicities
≥80%	Rash* (10%)	
50%–79%	Diarrhea Nausea	Increased CPK (4%)
20%–49%	Vomiting Abdominal pain (3%)	Musculoskeletal pain (5%) Headache (2%) COVID-19 (5%) Fatigue (2%) Peripheral neuropathy Increased triglycerides, cholesterol Decreased calcium Anemia Decreased hemoglobin

AEs occurring in ≥20% of patients; data for adult patients is not included.
*Rash includes dermatitis acneiform, eczema, maculo-papular rash, pustular rash, dermatitis, erythematous rash, palmar-plantar erythrodysesthesia syndrome, exfoliative rash, skin exfoliation, pruritic rash, papule, papular rash, and macular rash.

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Mirdametinib (package insert). Revised February 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219379Orig1s000lbl.pdf.

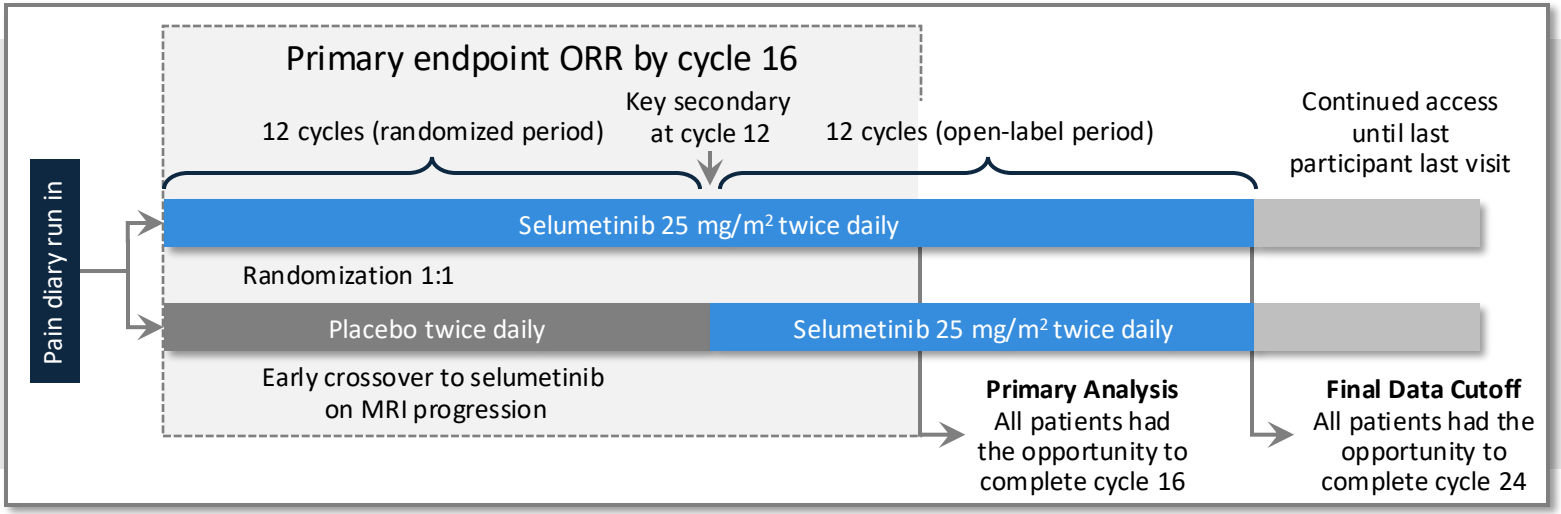
KOMET Trial

Selumetinib in Adults with Symptomatic Inoperable PN*

- Phase 3, placebo-controlled
- Adults ≥18 years of age
- NF1 + symptomatic inoperable PN
- A completed PAINS-pNF diary with a documented chronic target plexiform neurofibroma pain score on ≥4 of 7 days over ≥2 weeks during screening; stable chronic pain medication at baseline

Baseline Demographics (median values)

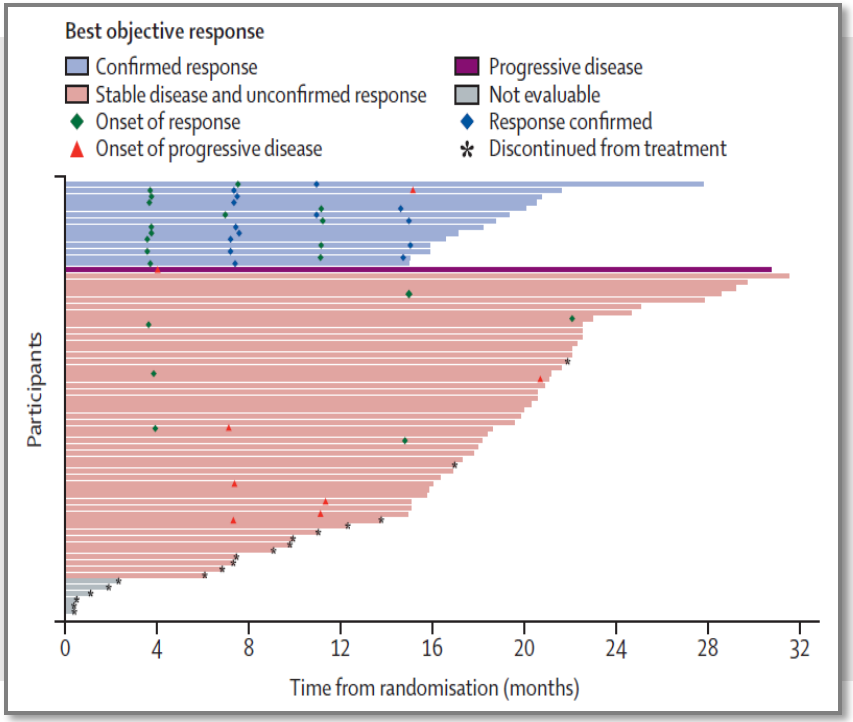
- Age: 29.5 years
- Male: 49%
- Volume of target PN: 92.0 mL selumetinib, 221.9 mL placebo
- Location of target PN
  - Neck + trunk (24%), trunk + limbs (24%), head (18%), head + neck (16%), trunk (10%), limbs (8%)
- Patients were stratified by chronic target plexiform neurofibroma pain score and geographical region

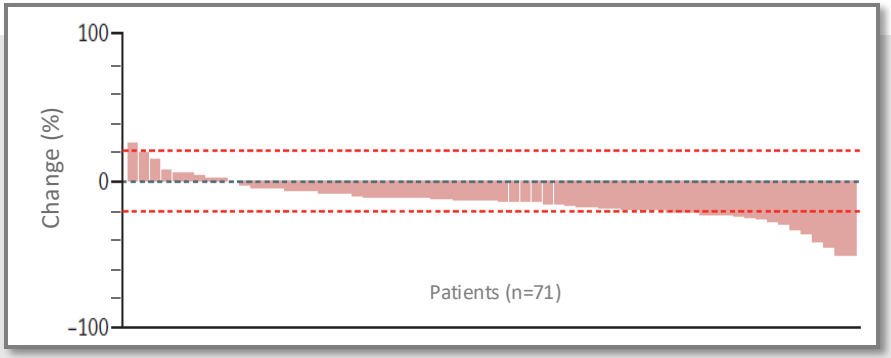


*Selumetinib is not FDA approved in adult patients who have a PN.

KOMET Trial: Efficacy

Selumetinib in Adults with Symptomatic Inoperable PN*





	Target plexiform neurofibroma volume, best percentage change	
Participants randomly assigned to selumetinib	Participants with an objective response by C16 (n=14)	Participants who had not reached an objective response by C16 (n=51)
Mean	−36·6	−9·9
Median (minimum, maximum)	−33·9 (−58·1 to −22·6)	−11·4 (−26·7 to 24·0)

*Selumetinib is not FDA approved in adult patients who have a PN.

Chen AP, et al. *Lancet*. 2025;405(10496):2217–2230.

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KOMET Trial: Adverse Events

	Selumetinib* n=71	Placebo n=74
Any AEs (grade ≥3)	100% (32%)	92% (18%)
Serious AE	14%	12%
AE leading to discontinuation	13%	7%
AE leading to dose modification	38%	14%
Any AE special interest	66%	22%
Maximum reported CTCAE grade		
1	23%	30%
2	45%	45%
3	27%	15%
4	6%	3%

	Selumetinib* n=71	Placebo n=74
Gastrointestinal disorders	75%	43%
Skin and subcutaneous tissue disorders	90%	35%
Musculoskeletal/connective tissue disorders	27%	23%
General disorders	51%	28%
Investigations	62%	28%
Infections and infestations	54%	45%
Eye disorders	17%	12%

All Grade (Grade 3–4)	Gastrointestinal	Skin and Subcutaneous Tissue	Other Toxicities
≥80%			
50%–79%	Diarrhea (12%)	Dermatitis acneiform (11%)	Increased CPK (5%)
20%–49%	Nausea (16%) Vomiting (8%)		

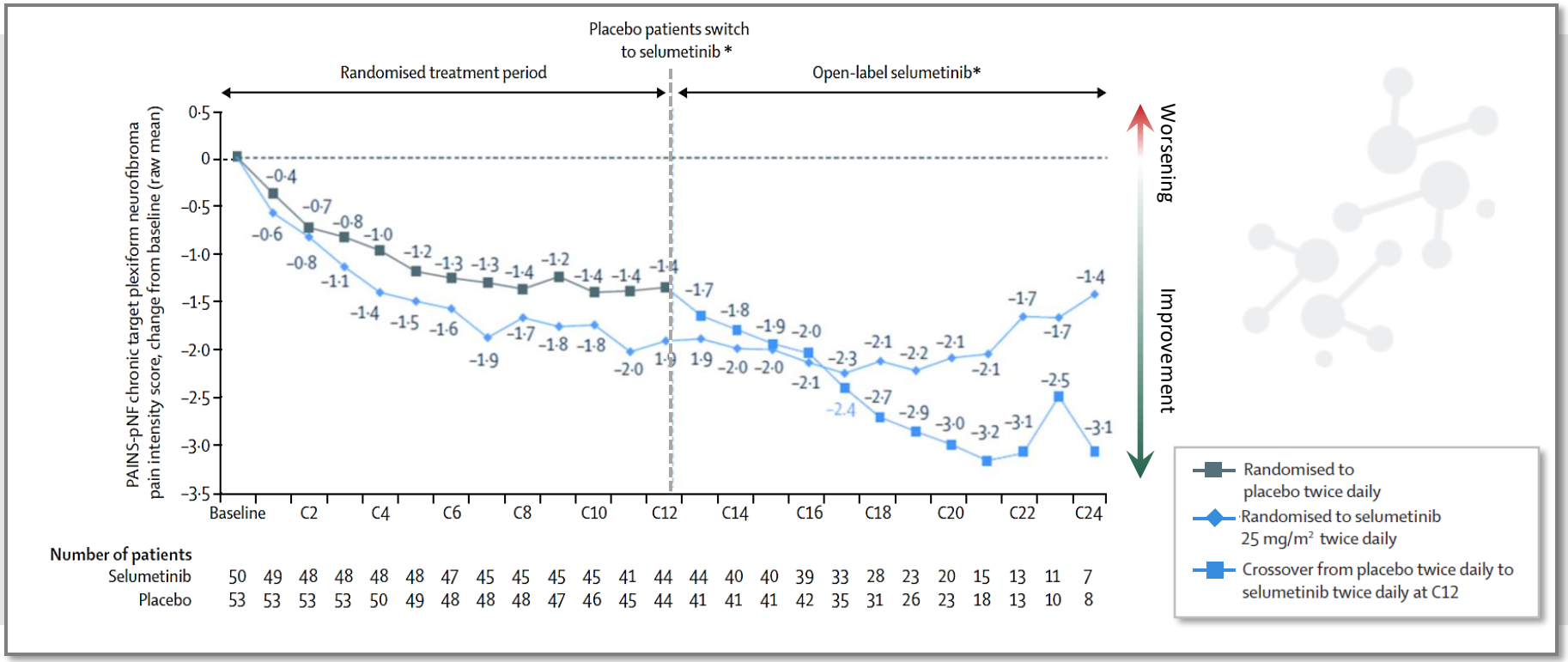
*Selumetinib is not FDA approved in adult patients who have a PN.

CTCAE, Common Terminology Criteria for Adverse Events.

Chen AP, et al. *Lancet*. 2025;405(10496):2217–2230.

KOMET Trial: Pain Scores

Selumetinib in Adults with Symptomatic Inoperable PN*



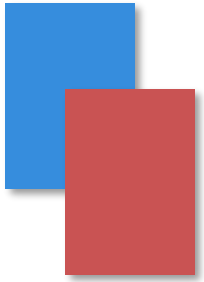
*Selumetinib is not FDA approved in adult patients who have a PN.

Chen AP, et al. *Lancet*. 2025;405(10496):2217–2230.

MEKi Options

SELUMETINIB*

- Pediatric patients
- Pill and granular (sprinkle) dosing
- Continuous therapy
- 6.2-hour serum half life
- Avoid CYP3A4 inhibitors



MIRDAMETINIB

- Pediatric and adult patients
- Liquid dosing
- 3 weeks on, 1 week off
- 28-hour serum half life

No head-to-head comparisons
No data on MEKi switching

*Selumetinib is not FDA approved in adult patients who have a PN.

Selumetinib (package insert). Revised January 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213756s004lbl.pdf.
Mirdametinib (package insert). Revised February 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219379Orig1s000lbl.pdf.

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Neurofibromatosis Type 1

Managing Patients Utilizing Long-Term MEK Inhibitor Therapy

Mary G. (…continued)



Mary receives mirdametinib. Her facial tumor shrinks to approximately half of its original size and the pain improves substantially. However, she develops grade 4 CPK increase.

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What is the next best step?

A. Assess for symptoms, if asymptomatic continue therapy
B. Switch to selumetinib
C. Withhold until grade ≤1 and resume at lower dose
D. Permanently discontinue treatment

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NF1-PN and MEKi Therapy Monitoring

Exam	Monitoring
Review of systems and physical examination (including GI, vision, skin, oral mucosa, and nails)	• Every visit (generally monthly)
Ophthalmologic examination	• Baseline, then every 6–12 months • Consider increased frequency with new symptoms
Echocardiogram/ejection fraction	• Baseline, every 3–6 months
Electrocardiogram	• Baseline, then as clinically indicated
Pregnancy status	• Baseline, then per institutional standards
Laboratory examinations	• Baseline, then every 3–6 months: creatine kinase, metabolic panel, liver function tests, CBC • Baseline, then as clinically indicated: amylase, lipase

CBC, complete blood count; GI, gastrointestinal.

Friedman JM. Neurofibromatosis 1. In: Adam MP, et al., eds. *GeneReviews*. Seattle (WA): University of Washington, Seattle; 1993 (updated 2025).
Moodley M, et al. *Semin Pediatr Neurol.* 2024;52:101172. Na B, et al. *Curr Oncol Rep*. 2024;26:706–713.
Lee TJ, et al. *Orphanet J Rare Dis.* 2023;18(1):292.

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General MEKi Safety Experience in Clinical Trials

Pediatric/Children

- Mild rash
- Paronychia
- Hypotonia or muscle weakness
- Retinal damage
- Impact on developmental changes are unknown

Adolescents/Adults

- Severe acne rash
- Paronychia
- Weight gain
- Fatigue
- GI problems

Gross AM, et al. *Nat Med*. 2025;31(1):105–115. Solares I, et al. *ESMO Open*. 2021;6(4):100223.
Gross AM, et al. *Neuro Oncol*. 2023;25:1883–1894. Moertel CL, et al. *J Clin Oncol*. 2025;43(6):716–729.

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Summary

- Patients with NF1 are at risk for tumor and nontumor manifestations, necessitating care from a multidisciplinary team
- PNs are one of the most common tumor manifestations in patients with NF1 and carry a significant risk of malignant transformation
- PN can be managed surgically, with MEKis, or on clinical trial
- Many areas of ongoing research to improve therapy for patients with NF1-PN
- The goal of transition of care is to maintain optimal healthcare, which can only be achieved when each person, at every age, receives medically and developmentally appropriate care

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The Future

NCT Number	Phase II Study Title	Study Status	Conditions	Primary Outcome Measures	Age Group
NCT05331105	HL-085 in Adults with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas	Recruiting	NF1-PN	ORR	Adult, older adult
NCT06541847	INSPIRE: A Phase 2, Open-Label Study to Evaluate the Safety and Effects of HLX-1502 in Patients with Neurofibromatosis Type 1	Recruiting	NF1	PN response rate	Child, adult, older adult
NCT06188741	NF114: Selumetinib for the Prevention of Plexiform Neurofibroma Growth in NF Type 1	Not yet recruiting	NF1-PN	PFS	Child

ClinicalTrials.gov.

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Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

- *Refer patients to NF1 centers.* NF1 is a complex disease that requires support from many specialists. NF1 centers offer access to experts with experience in managing the specific needs of these patients.
- *Develop a robust multidisciplinary team for NF1 patient care.* Clinicians should have a low threshold for calling in support from specialists in neurology, cardiology, nephrology, pulmonology, genetics, and other specialties.
- *Implement strategies to improve transitions from pediatric care and integration into adult care.* Patients with NF1 are typically diagnosed in childhood and will need to transition to managing their own care as adults, which may be challenging for a young person. Remember, it is not too early to plan for the future.

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To Ask a Question

To submit a question, please go to the *Ask Question* tab at the bottom of the screen.

Additional Resources

Visit www.ceconcepts.com for clinical information and certified educational activities.

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Scan the appropriate QR code for your mode of participation in this activity and create or log in to a Creative Educational Concepts learner account. Complete the necessary requirements (e.g., pre-test, post-test, evaluation) and then claim your credit.*

Thank you for your participation!

*To receive credit, participants must register an account and apply for credit within 10 days of the live activity. For questions or technical difficulties, please contact info@ceconcepts.com.

In-Person

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3 Steps to Complete

1. Actively participate in the discussion today by **responding to questions** and/or **asking the faculty questions**
   (MOC credit can be claimed even if a question goes unanswered or an incorrect response is entered)
2. Complete the post-test and evaluation at the conclusion of the webcast
3. Enter your **ABIM ID number** and **DOB** (MM/DD) on the evaluation, so credit can be submitted to ABIM

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How to Claim This Activity as a CME for MIPS Improvement Activity

- Actively participate today by responding to ARS questions and/or asking the faculty questions
- Complete the post-test and activity evaluation at the link provided
- Over the next 3 months, actively work to incorporate improvements from this presentation into your clinical practice
- In approximately 3 months, complete the follow-up survey from Creative Educational Concepts

CME for MIPS IMPROVEMENT ACTIVITY

CEC will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity.

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THE MEKTRIX

DECODING THE REAL-WORLD IMPACT OF THERAPEUTIC ADVANCES IN NEUROFIBROMATOSIS TYPE 1–ASSOCIATED PLEXIFORM NEUROFIBROMA MANAGEMENT ACROSS PEDIATRIC AND ADULT POPULATIONS

This program is supported through an independent educational grant from SpringWorks Therapeutics, Inc.