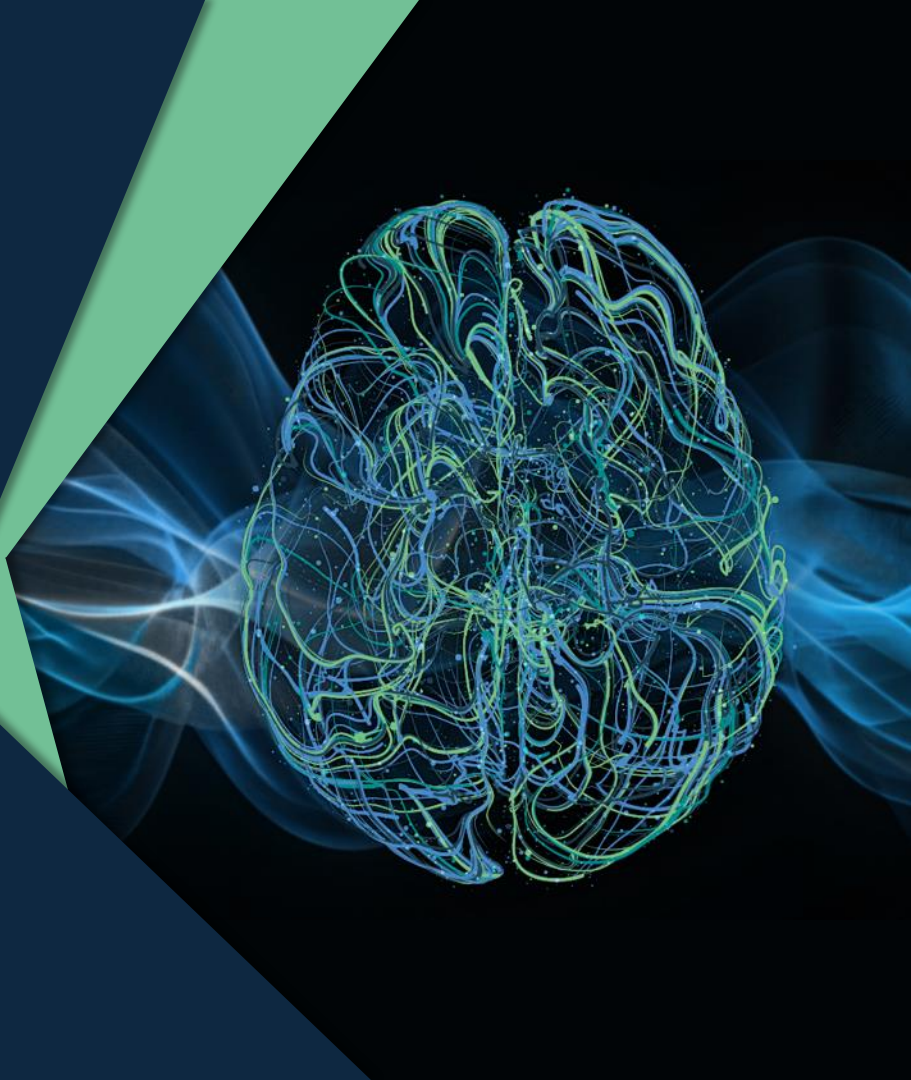
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MEK INHIBITORS IN NEUROFIBROMATOSIS TYPE 1

LATEST ADVANCES AND REAL-WORLD APPLICATIONS IN NF1-PN MANAGEMENT



This program is supported through independent educational grants from Alexion Pharmaceuticals and SpringWorks Therapeutics, Inc.



In support of improving patient care, Creative Educational Concepts LLC (CEC) is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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This activity was planned by and for the healthcare team, and learners will receive 1.0 Interprofessional Continuing Education Credit for learning and change.

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The program content has been reviewed by the Oncology Nursing Certification Corporation (ONCC) and is acceptable for recertification points.

OCN
Care Continuum
Oncology Nursing Practice
Psychosocial Dimensions of Care
Symptom Management, Palliative Care, Supportive Care Treatment

CBCN
Care Continuum
Psychosocial Dimensions of Care
Treatment

BMTCN
Professional Practice/Performance

CPHON
Care Continuum
Care of the Pediatric Hematology and Oncology Patient
Psychosocial Dimensions of Care
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

Certificate of Participation

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Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

CME for MIPS IMPROVEMENT ACTIVITY

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The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any uses not approved by the FDA) of products or devices.

To Ask a Question

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



Angela Hirbe, MD, PhD

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Disclosures

FACULTY

Angela Hirbe, MD, PhD, reports the following financial relationships:

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

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PATIENT ADVOCATES/PLANNERS

Evan Neale reports no financial relationships to disclose

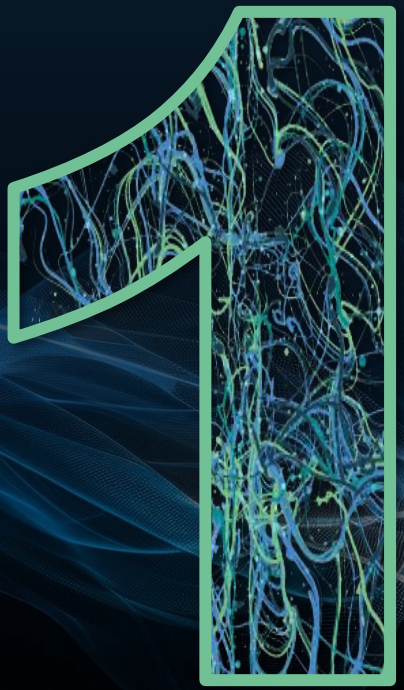
Sarah Neale reports no financial relationships to disclose

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- Alaa Bawaneh, MD, PhD (peer reviewer)
- Andrea Edwards, PA-C (peer reviewer)
- David Modrak, PhD (planning committee)
- Nichole Lainhart (planning committee)
- Scott J. Hershman, MD, FACEHP, CHCP (planning committee)
- Sandra Caballero, PharmD (planning committee)
- Sharon Tordoff (planning committee)

All identified conflicts of interest have been mitigated.

LEARNING OBJECTIVE



Identify key characteristics of neurofibromatosis type 1 (NF1) clinical presentation and disease advancement across the lifespan, including genetic etiology and multisystem pathophysiology of NF1, that impact early and accurate diagnosis

LEARNING OBJECTIVE



Integrate MEK inhibitors in the management of NF1-associated plexiform neurofibromas (PNs) in pediatric patients

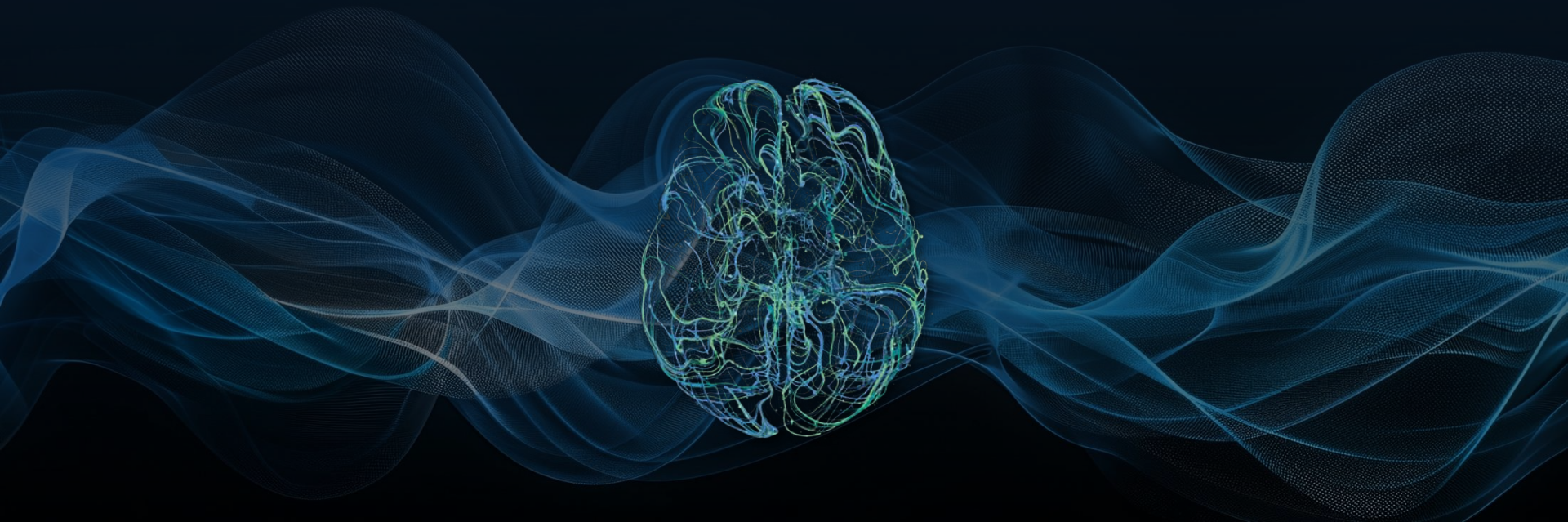
LEARNING OBJECTIVE



Develop comprehensive care plans that include disease monitoring, managing toxicities, and personalized treatment for patients with NF1 across the lifespan

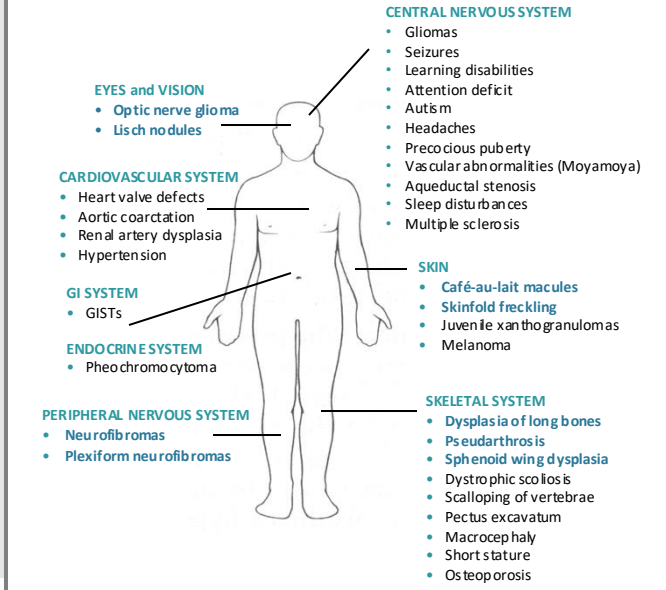
Neurofibromatosis Type 1

Clinical Features and Diagnostic Criteria



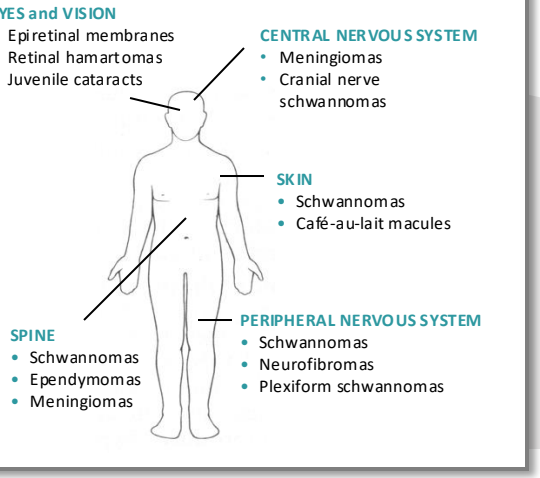
Neurofibromatosis

NEUROFIBROMATOSIS TYPE 1 (NF1)



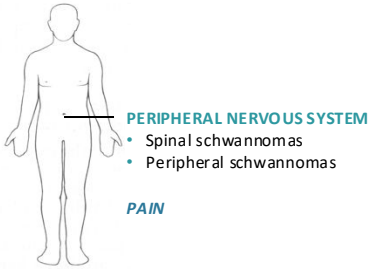
1 in 2,800 people worldwide

NF2-RELATED SCHWANNOMATOSIS (NF2)



1 in 67,700 people worldwide

NON-NF2 SCHWANNOMATOSIS



1 in 158,000 people worldwide

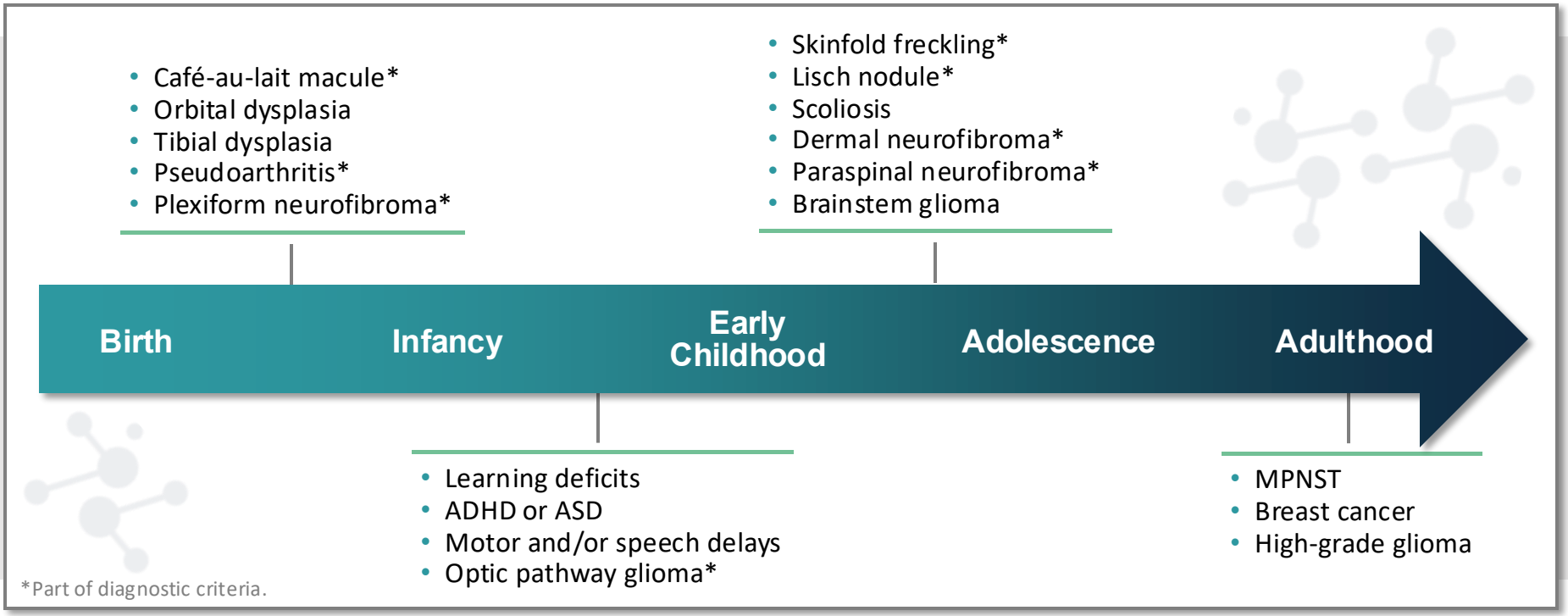
GIST, gastrointestinal stromal tumors.

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



ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; MPNST, malignant peripheral nerve sheath tumors; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.

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



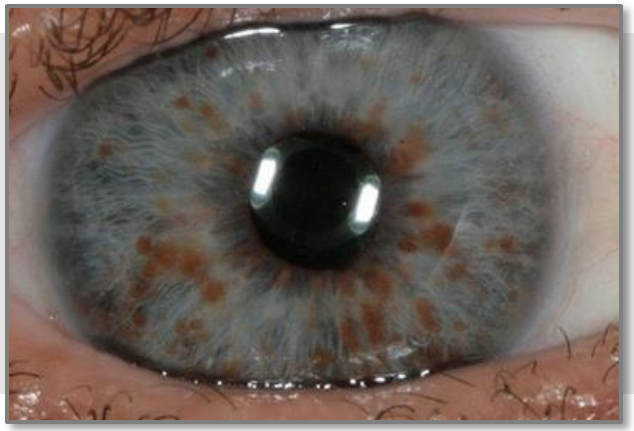
- Present in ~75% of patients
- Usually detected by 5–8 years of age

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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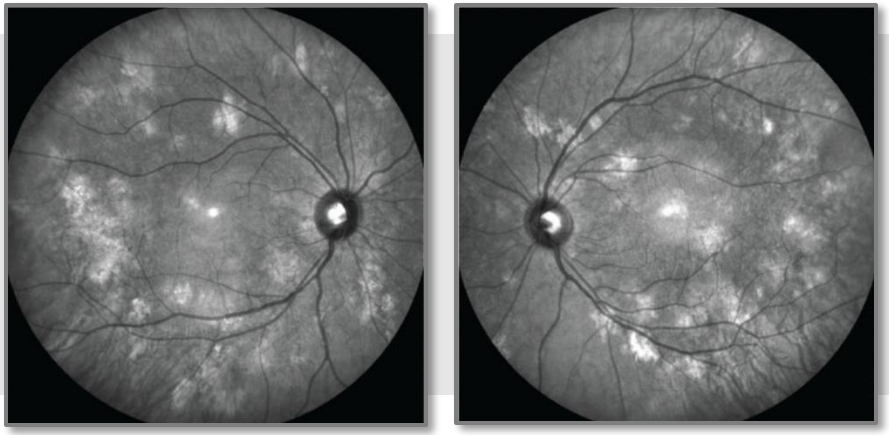
NF1
Ocular Abnormalities

Lisch Nodules



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

Choroidal Abnormalities



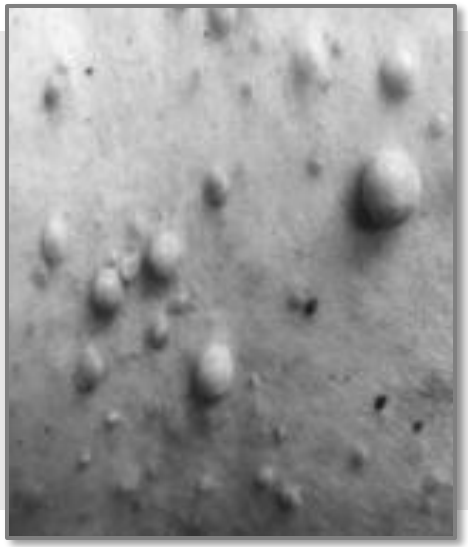
NIR imaging

- 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.

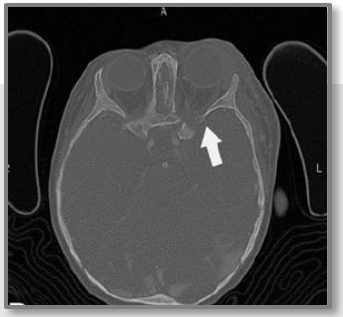
NF1
Additional Manifestations

Dermal Neurofibromas



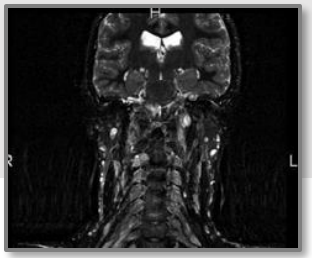
Dysplasia of Tibia and Sphenoid Bone





Cervical and Brachial PN





Optic Pathway Glioma



PN, plexiform neurofibroma.

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

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:

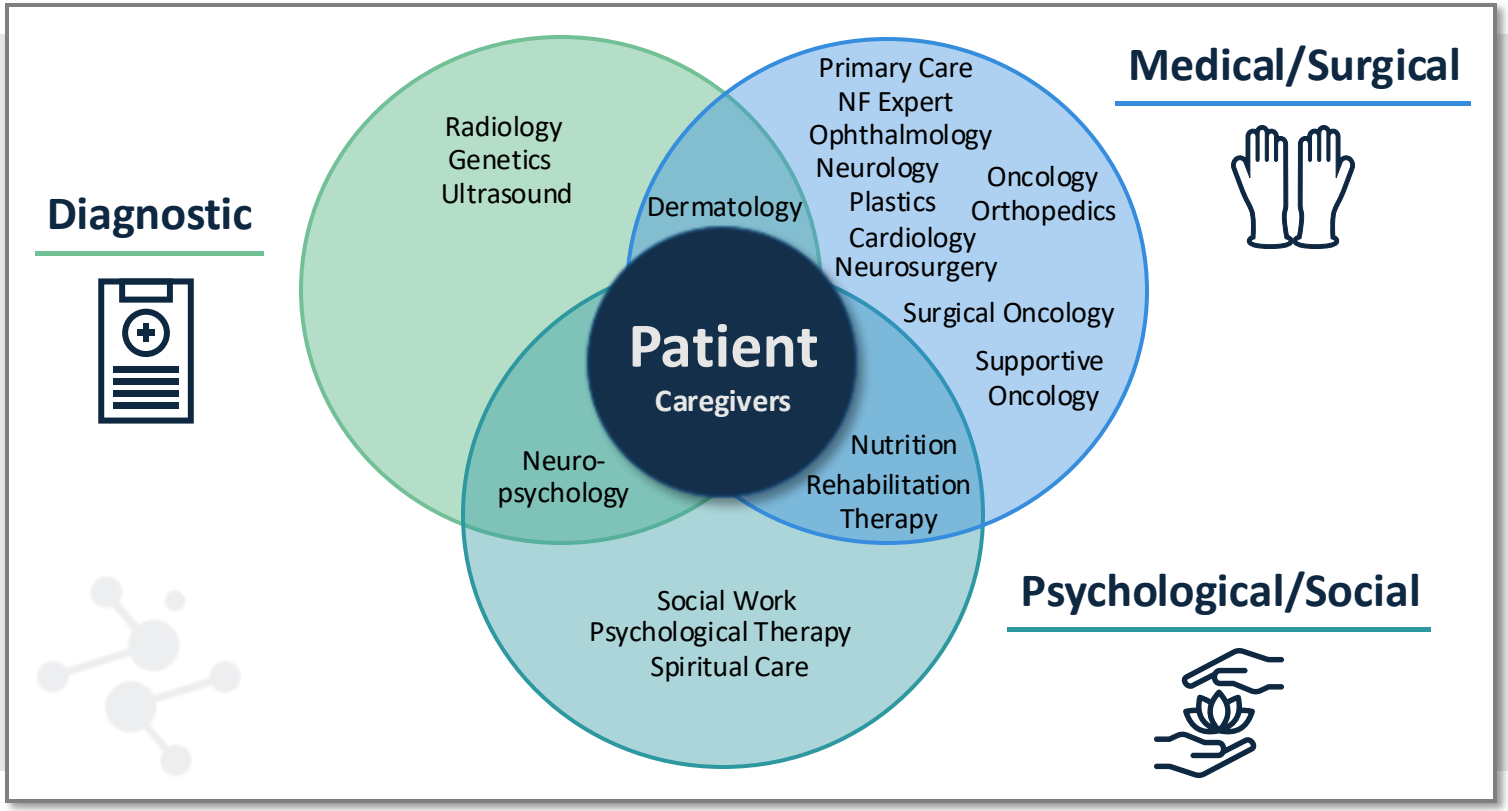
1. Six or more café-au-lait spots (in the greatest diameter)
   - 1.5 cm or larger after puberty
   - 0.5 cm or larger before puberty
2. Freckling in the axilla or groin
3. Two or more neurofibromas OR one plexiform neurofibroma
4. Optic pathway glioma
5. Two or more iris Lisch nodules OR **two or more 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.

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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.

Case: Olivia M.



Olivia M. is a 6-year-old female referred for evaluation of mild developmental delays and behavioral concerns. She had delayed expressive language and is currently struggling in school. Her kindergarten teacher and parents report signs of possible ADHD and social anxiety.

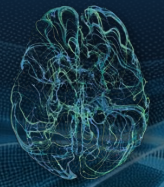
Behavioral issues include poor attention span, frequent emotional outbursts, and difficulty with fine motor tasks and peer interaction.

Mother with café-au-lait spots and scoliosis, no confirmed NF1 diagnosis; no known malignancies or seizures in immediate family.

Examination reveals:

- 9 café-au-lait spots >0.5 cm (largest 1.5 cm, multiple smaller spots)
- Bilateral axillary freckling, no neurofibromas palpable
- No visible Lisch nodules
- Mild hypotonia, coordination difficulty noted
- Mild scoliosis on Adam's forward bend test; no long bone abnormalities
- Visual-spatial and processing deficits, attention and executive function concerns

What do you recommend for this patient?



1. Continued typical pediatric care
2. Genetic evaluation
3. Neuropsychological testing
4. Occupational therapy
5. Speech-language pathology testing
6. Behavioral therapy
7. MRI scans of brain/orbits
8. Normal monitoring of growth and development
9. Recommend school support (Individualized Education Plan [IEP] or 504 plan)
10. Regular monitoring by primary care

Olivia M. (…continued)



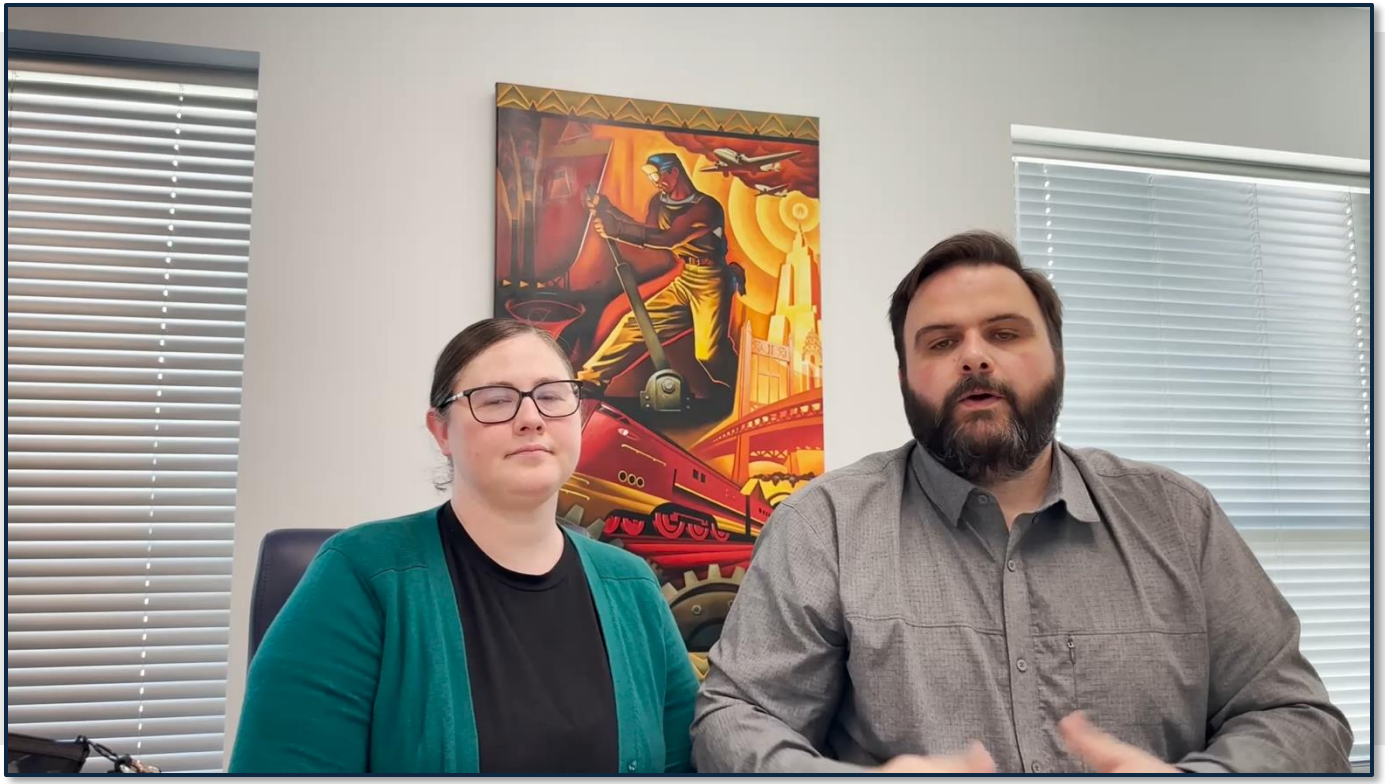
Recommendations

- Genetic testing for NF1 confirmation
- 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

Importance of Prompt Diagnosis

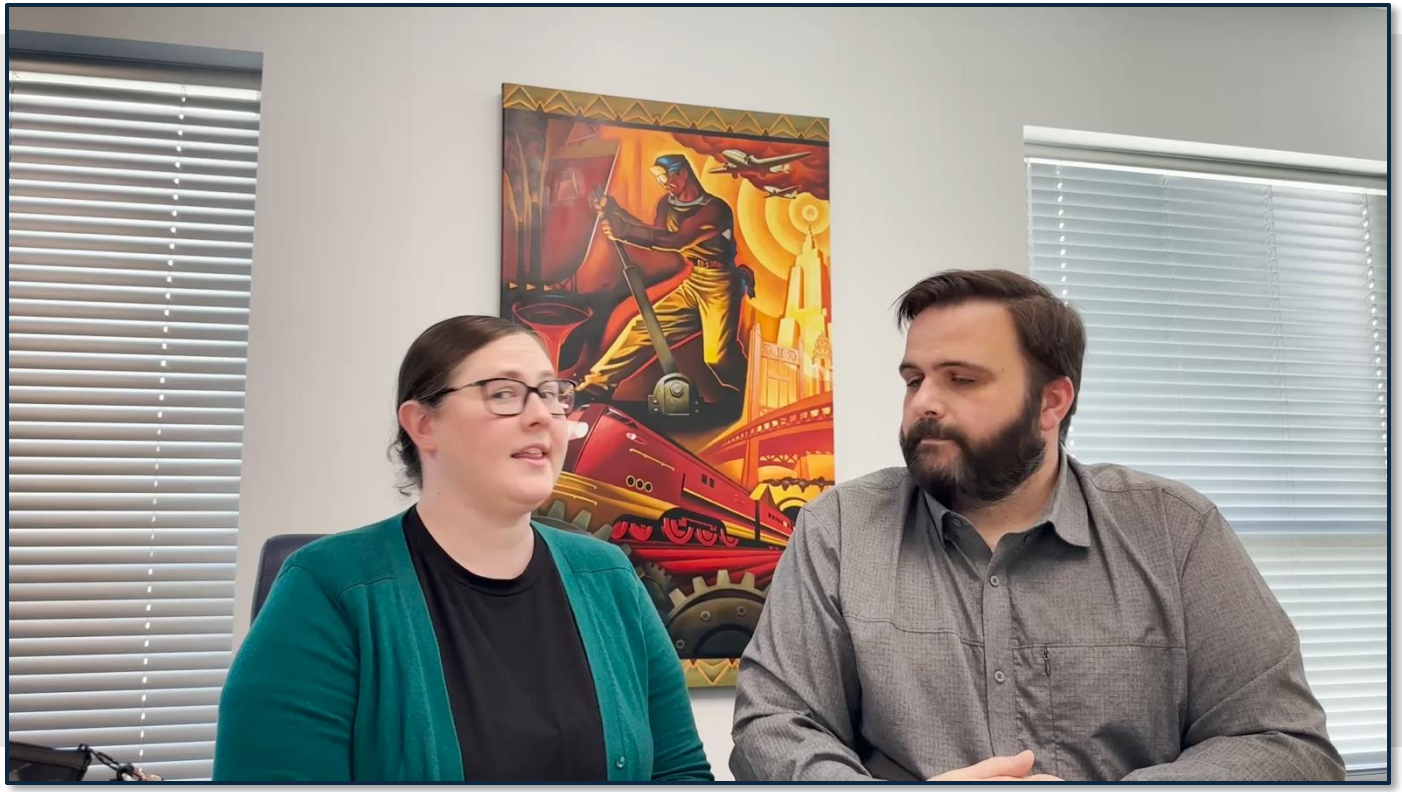
Sarah Neale
Patient Advocate
Mother to NF Warrior, Declan

Evan Neale
Patient Advocate
Member, CTF Engage



Importance of Involving Care Specialists

Sarah Neale
and Evan Neale
Patient Advocates

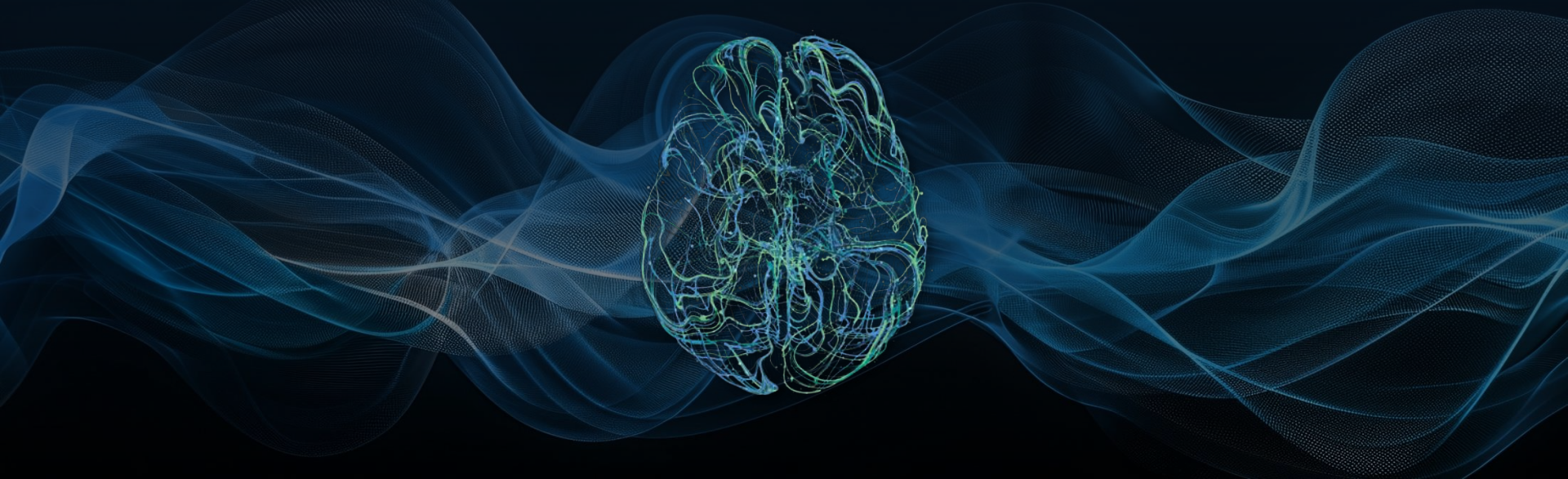


Common Missed Opportunities

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

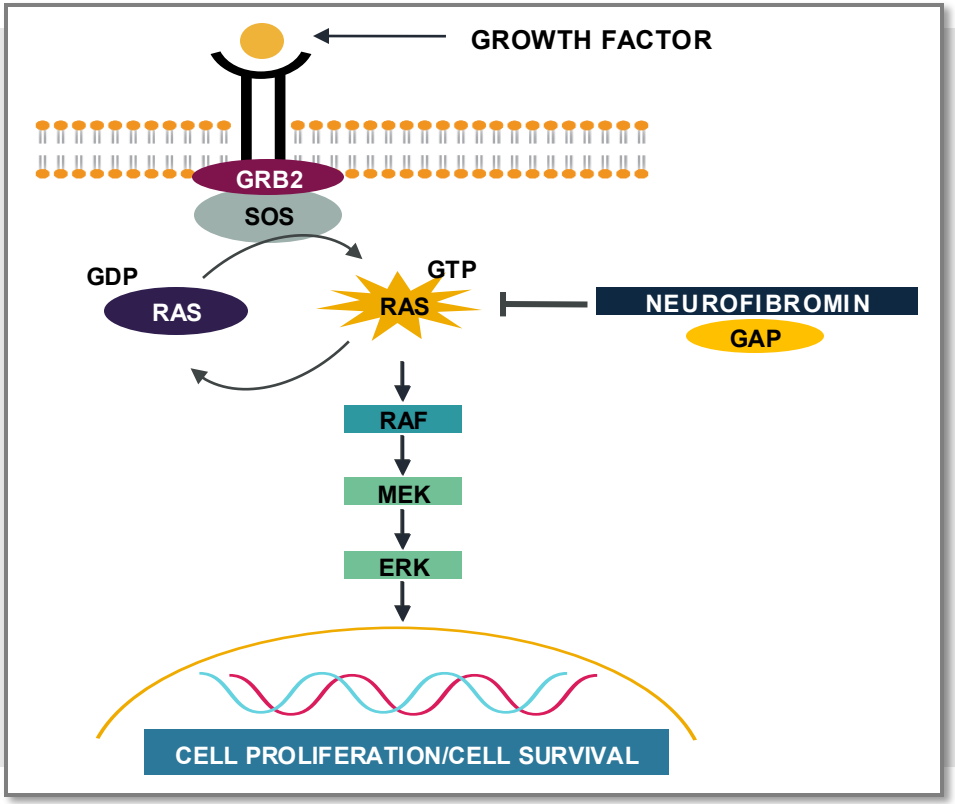
Neurofibromatosis Type 1

MEK Inhibitors for the Treatment of Symptomatic, Inoperable Plexiform Neurofibromas



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-Plexiform Neurofibromas (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.

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.

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.

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%
- Permeant 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.

Olivia M. (…continued)



Olivia is diagnosed with NF1 and receives supportive care.



At 13 years of age, she is diagnosed with a plexiform neurofibroma in the left carotid space. She has no pain, issues with range of motion, problems swallowing, or respiratory distress. She continues supportive care and observation for her PN.



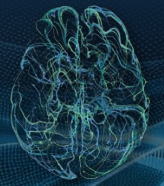
Repeat imaging by NF1 clinic demonstrates slowly increasing size over subsequent years plus appearance of new dermal PNs.



At 16 years of age, the neck PN becomes symptomatic and interferes with QoL.

QoL, quality of life.

Which do you recommend for this patient?



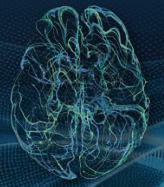
A. Continued observation
B. Multi-D tumor board
C. Surgery
D. Radiation therapy
E. Systemic therapy



Recommendations

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

Which agent would you recommend?



A. Carboplatin + vincristine
B. Ifosfamide + doxorubicin
C. MEK inhibitor
D. Temozolomide

Targeted Medical Therapy for NF1-PN

Several MEKi and tyrosine kinase inhibitors have demonstrated activity against NF1-PN.

Outcomes of note in clinical trials:

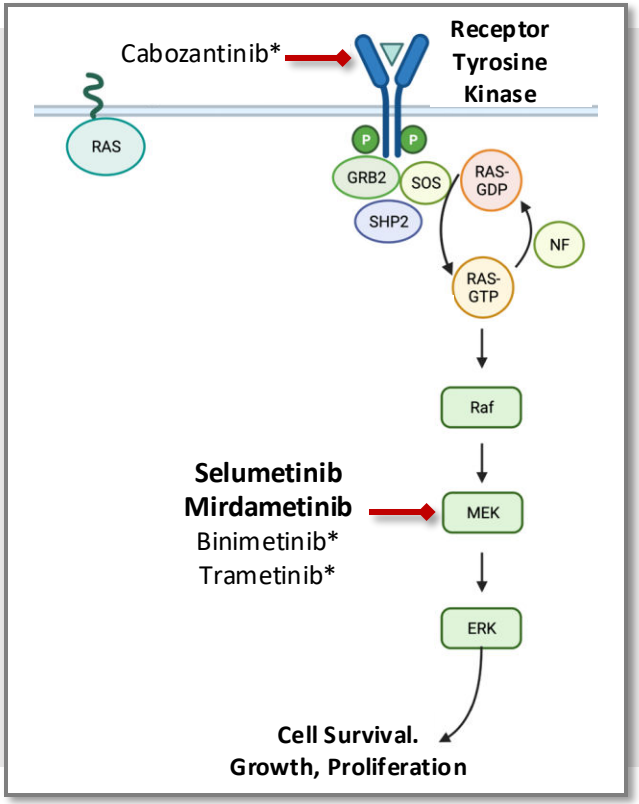
- Assessed PN growth and response via 3D volumetric analysis
- Patient-reported and functional outcome assessments

SELUMETINIB

Pediatric patients 2 years of age and older with NF1 who have symptomatic, inoperable PN

MIRDAMETINIB

Adult and pediatric patients 2 years of age and older with NF1 who have symptomatic PN not amenable to complete resection

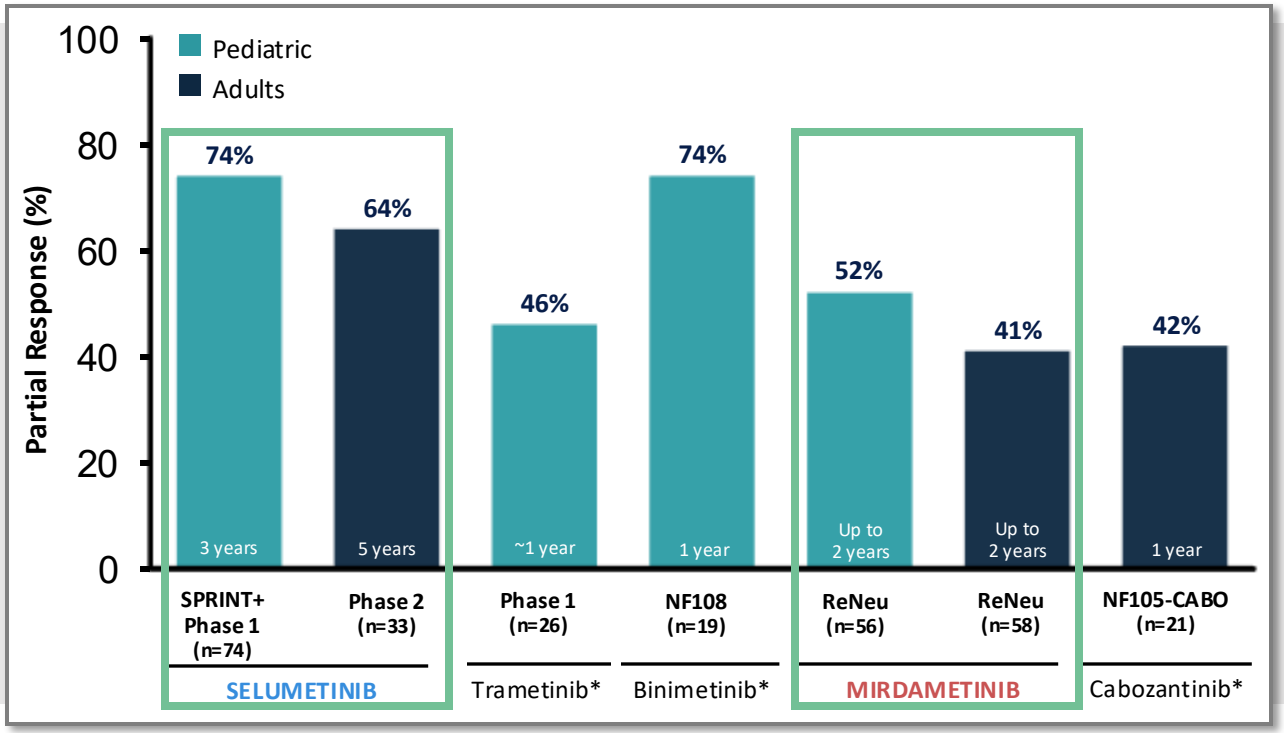


*Not FDA approved for the treatment of NF1-PN.

MEKi, mitogen-activated kinase inhibitor; 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.

Overview of Reported Partial Response Rates with MEKi 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

*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.

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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

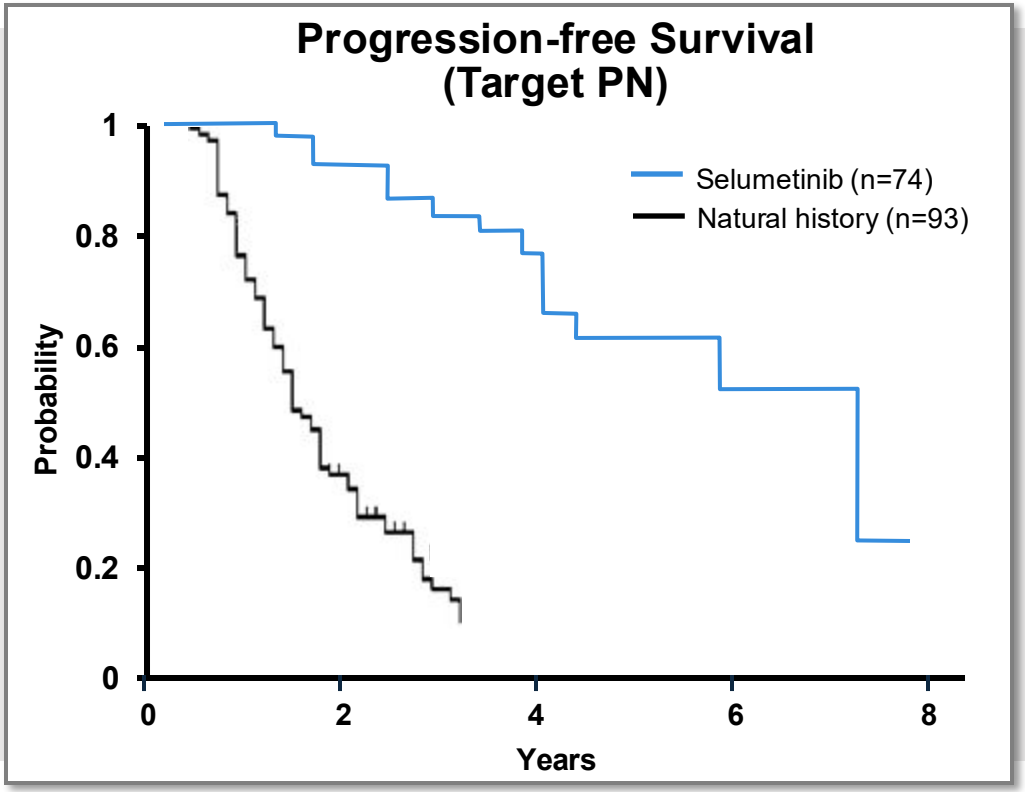
Gross AM, et al. *N Engl J Med*. 2020;382:1430–1442.

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Combined 5-year Progression-free Survival

SPRINT + Phase I

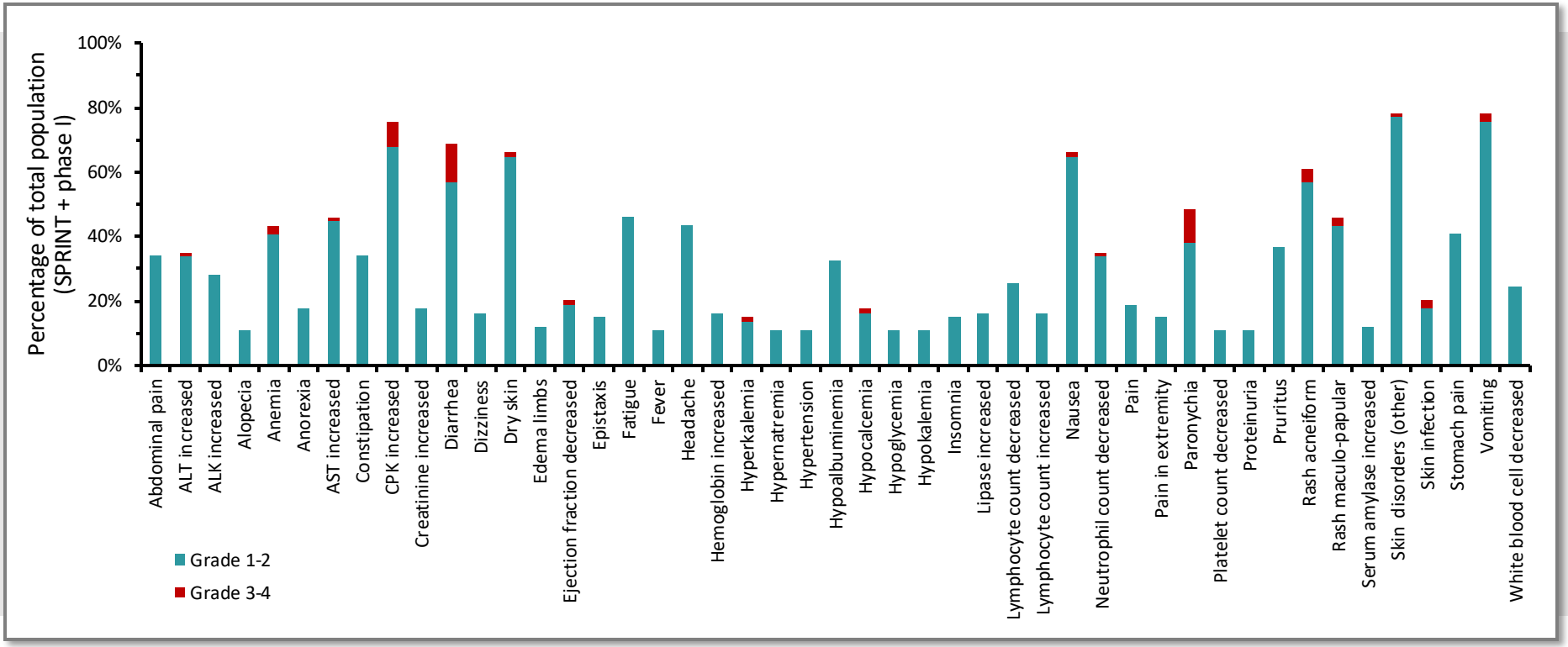
- Combined cohort (n=74)
  - Continuous selumetinib dosing (median duration: 57.5 cycles)
  - Remaining on treatment at data cutoff (n=31)
- Partial response
  - Confirmed and durable: 70% and 59%
- Time to response (median)
  - Initial: 8 cycles (range 4–40)
  - Best response: 18 cycles (range 4–94)
- 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. *Nat Med.* 2025;31(1):105–115.

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Selumetinib Adverse Events



AEs occurring in ≥10% of patients

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

AE, adverse event.

Gross AM, et al. *Nat Med.* 2025;31(1):105–115.

Selumetinib
Warnings and Precautions

BOXED WARNINGS

- Ocular toxicity: blurred vision, photophobia, cataracts, and ocular hypertension
  - 15% of pediatric population (resolved in 82%)
- Left ventricular dysfunction
  - Decreased LVEF of ≥10% occurred in 23% of pediatric patients (all were identified during routine echocardiography); decreased LVEF resolved in 71% of these patients
- Dermatological AEs
  - 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)
- 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:

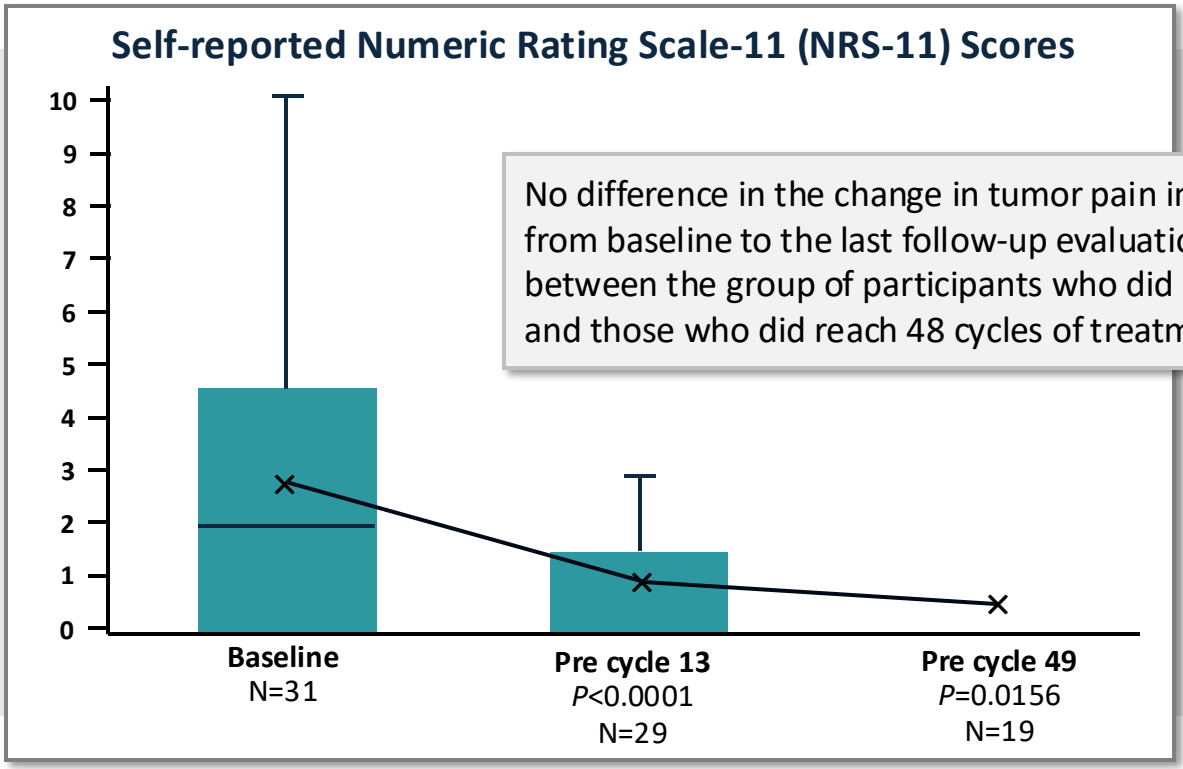
- Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED)
- Intestinal perforation, colitis, ileus, and obstruction
- Cardiomyopathy (decreased LVEF)
- Severe palmar-plantar erythrodysesthesia syndrome
- Rhabdomyolysis

*Selumetinib is not FDA approved in the adult population

LVEF, left ventricular ejection fraction.

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

Selumetinib
Patient-reported Pain



Gross AM, et al. *Nat Med*. 2025;31(1):105–115.

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

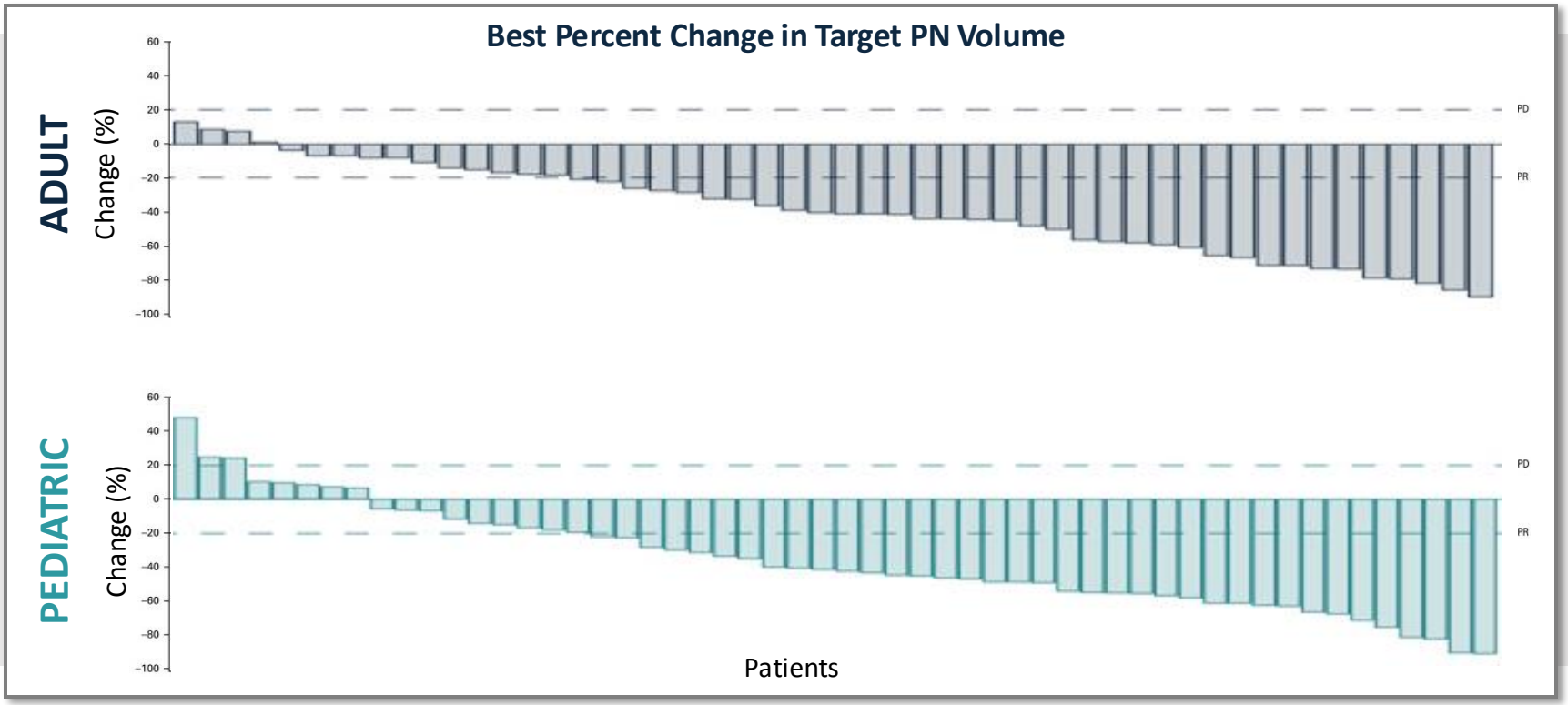
BID, twice daily; MRI, magnetic resonance imaging; QoL, quality of life.

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

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Mirdametinib (ReNeu)

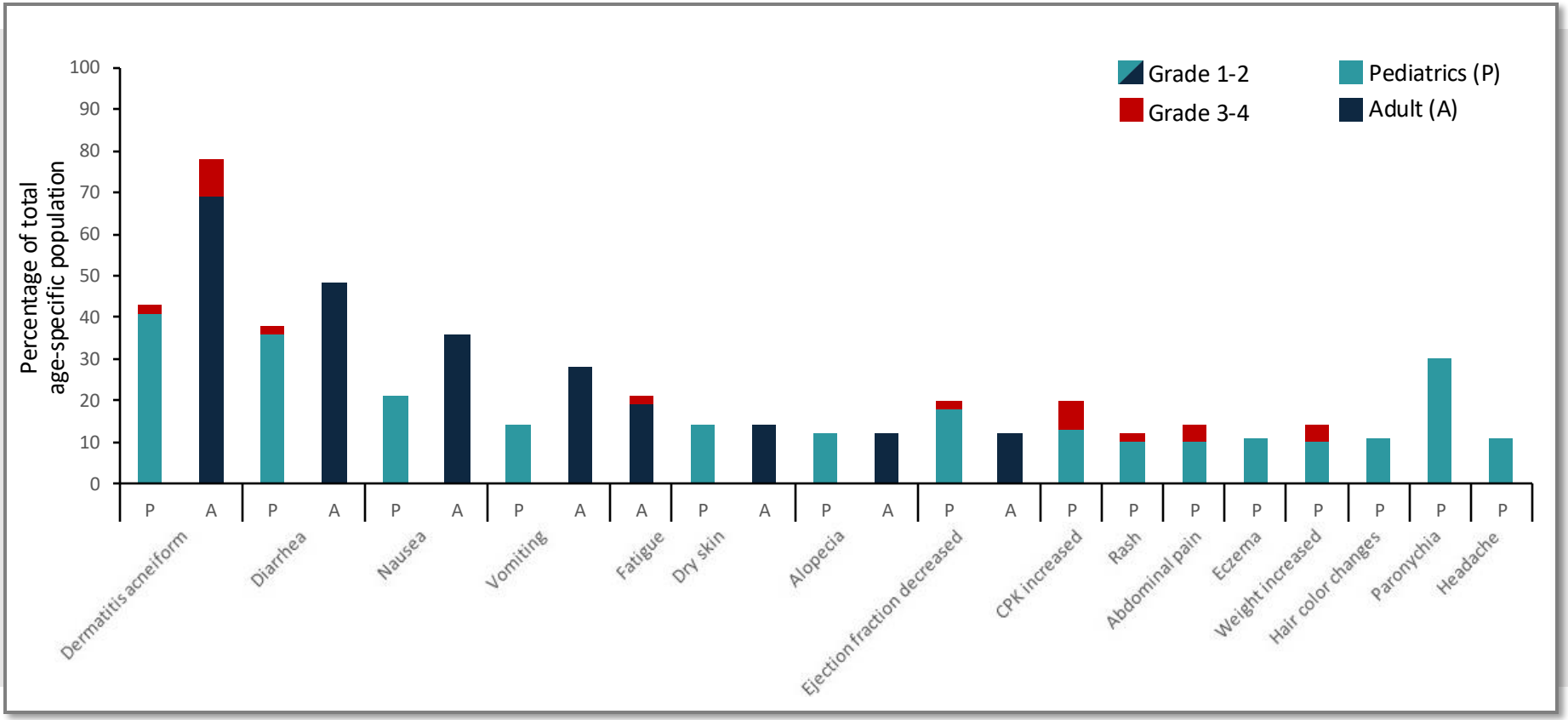
Best Change from Baseline in Target PN Volume per Patient



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

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Mirdametinib Adverse Events



AEs occurring in ≥10% of patients

Mirdametinib
Warnings and Precautions

BOXED WARNINGS

- Ocular toxicity: retinal vein occlusion (RVO), retinal pigment epithelium detachment (RPED), and blurred vision
  - Occurred in 25% of patients; 25% 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

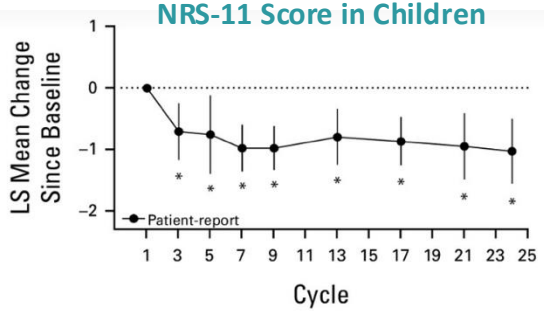
Mirdametinib (package insert). Revised February 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219379Orig1s000lbl.pdf.

Mirdametinib (ReNeu)

Pain and QoL

Patient-reported Pain

NRS-11 Score in Children

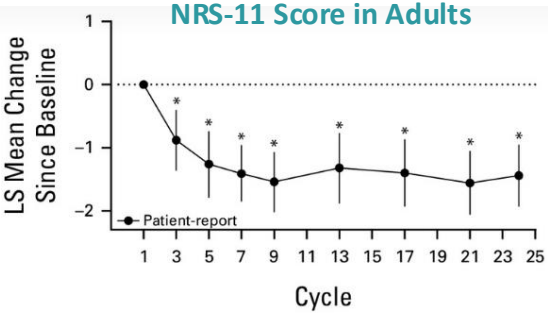


No. patients

Patient-report	36	23	25	24	23	17	18	11	8

Worsening ↑ ↓ Improving

NRS-11 Score in Adults

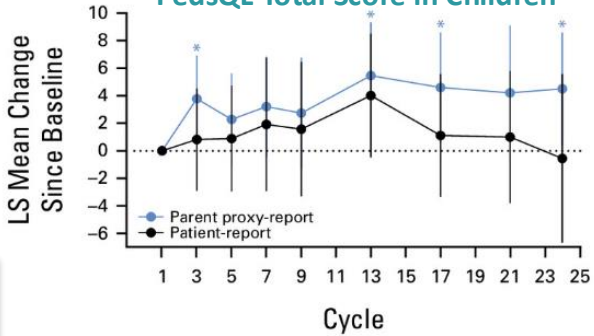


No. patients

Patient-report	51	42	37	36	35	21	21	16	17

Patient-reported QoL

PedsQL Total Score in Children

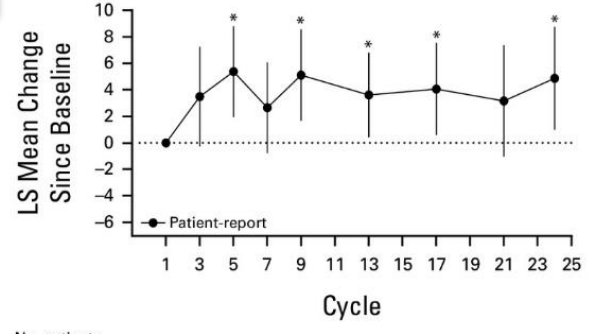


No. patients

Patient-report	50	48	47	41	42	38	34	32	29
Parent proxy-report	55	52	52	48	47	43	36	36	33

Improving ↑ ↓ Worsening

PedsQL Total Score in Adults

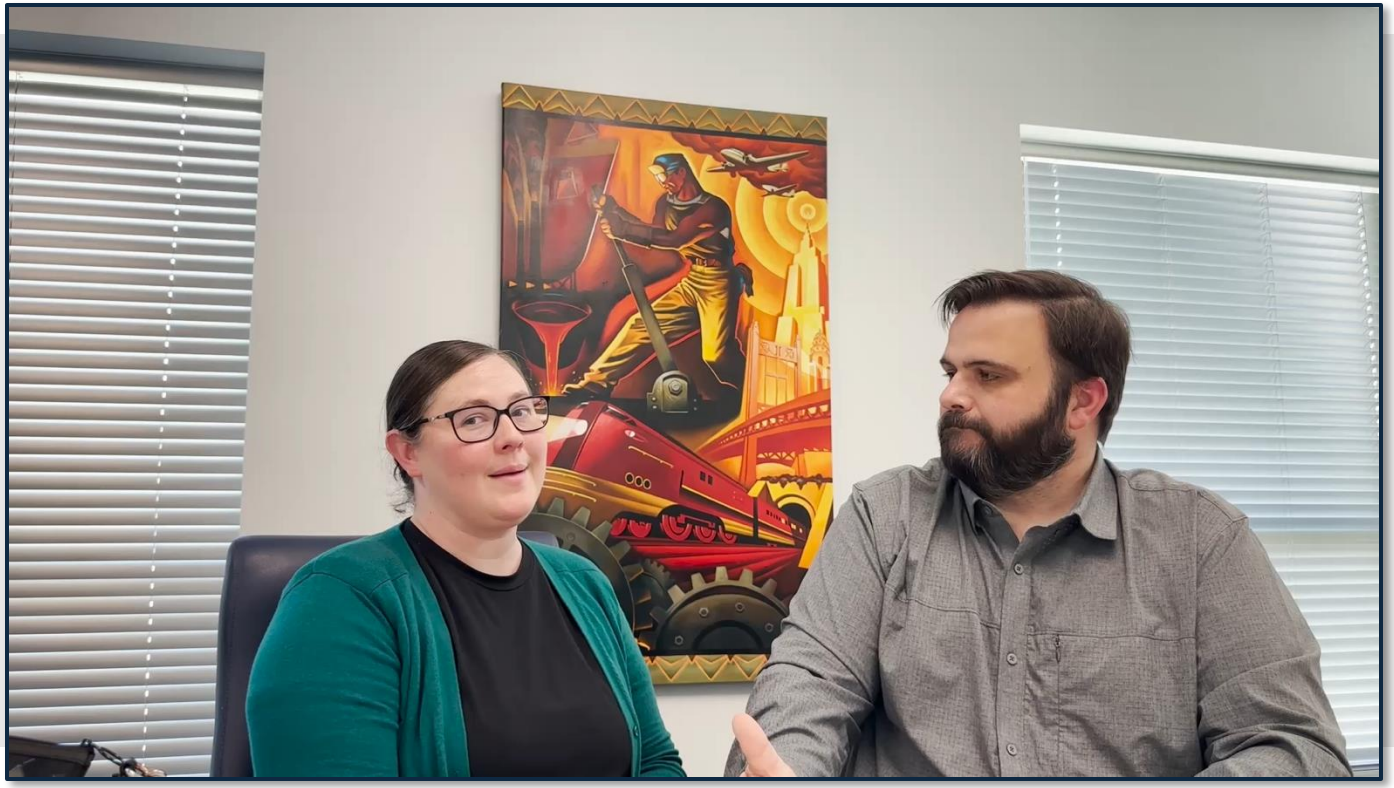


No. patients

Patient-report	55	48	46	44	44	34	32	28	28

Concerns about Long-term Treatment

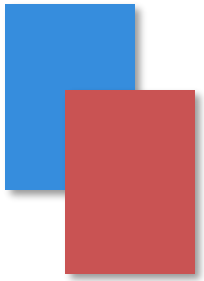
Sarah Neale
and Evan Neale
Patient Advocates



Comparison of MEKi Options

SELUMETINIB

- Pediatric patients
- Pill 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 (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.

Neurofibromatosis Type 1

Managing Patients Utilizing Long-term MEK Inhibitor Therapy



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.

General MEKi Safety Experience in Clinical Trials

Pediatric/Children

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

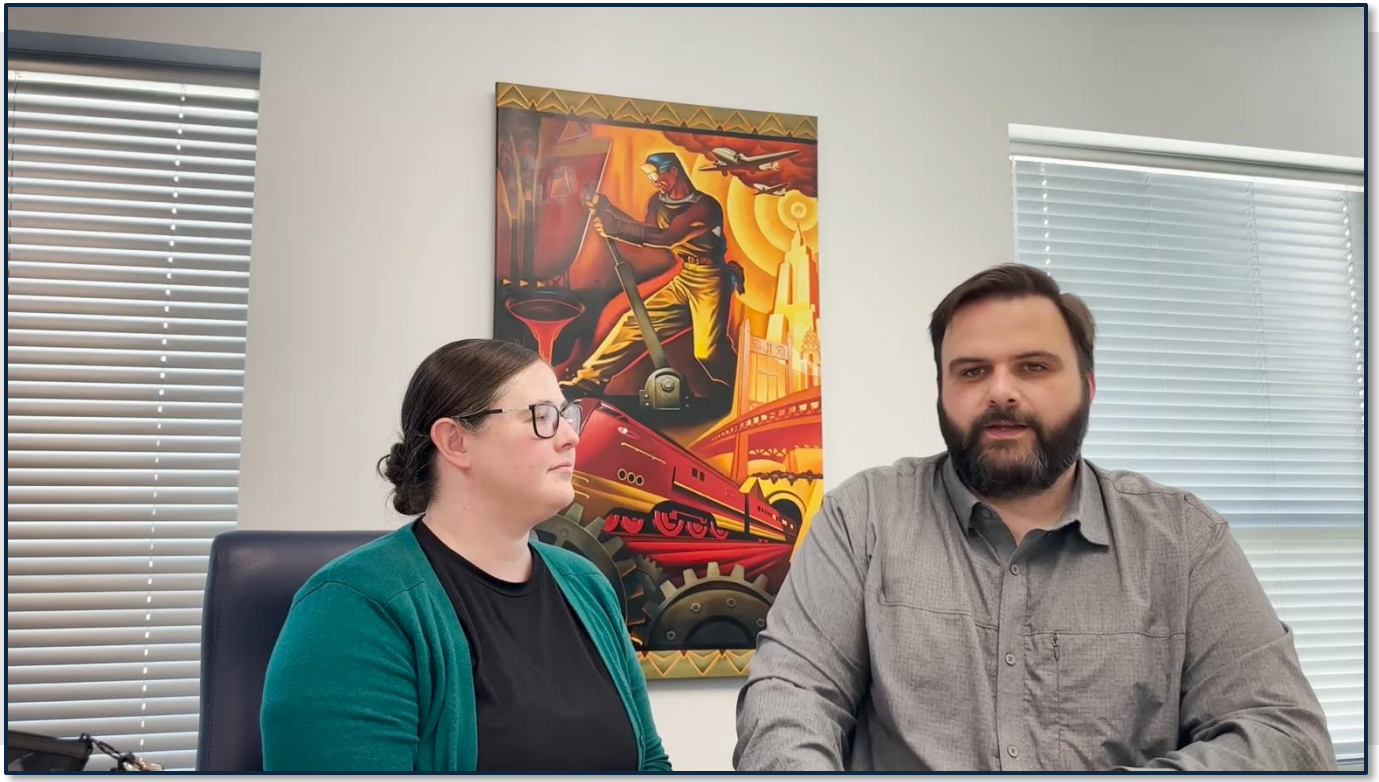
Adolescents/Adults

- 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.

Concerns about Drug Holidays

Sarah Neale
and Evan Neale
Patient Advocates



Drug Holidays

- PN therapy requires MEKi exposure over long periods of time (maximum response achieved up to 2 years after treatment initiation)
- Pauses to MEK inhibitor therapy in patients with NF1 and PNs
  - Decisions should be individualized, carefully considered, and closely monitored
  - Potential for tumor regrowth necessitates a cautious approach
  - Readiness to resume treatment if needed
- Efficacy should be weighed against toxicity: monitor for toxicity and thoroughly assess pain and QoL

Solares I, et al. *ESMO Open*. 2021;6(4):100223.

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 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.

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

1 TRANSITION POLICY



Ages 12–14

- Discuss transition policy with patient and family

2 TRANSITION TRACKING AND MONITORING



Ages 14–18

- Track progress

3 TRANSITION READINESS



- Assess skills

4 TRANSITION PLANNING



- Develop healthcare transition plan, including medical summary

5 TRANSFER/ INTEGRATE INTO ADULT-CENTERED CARE



Ages 18–21

- Transfer to adult-centered care
- Integration into adult practice

6 TRANSITION COMPLETION AND ONGOING CARE WITH ADULT CLINICIAN



Ages 18–26

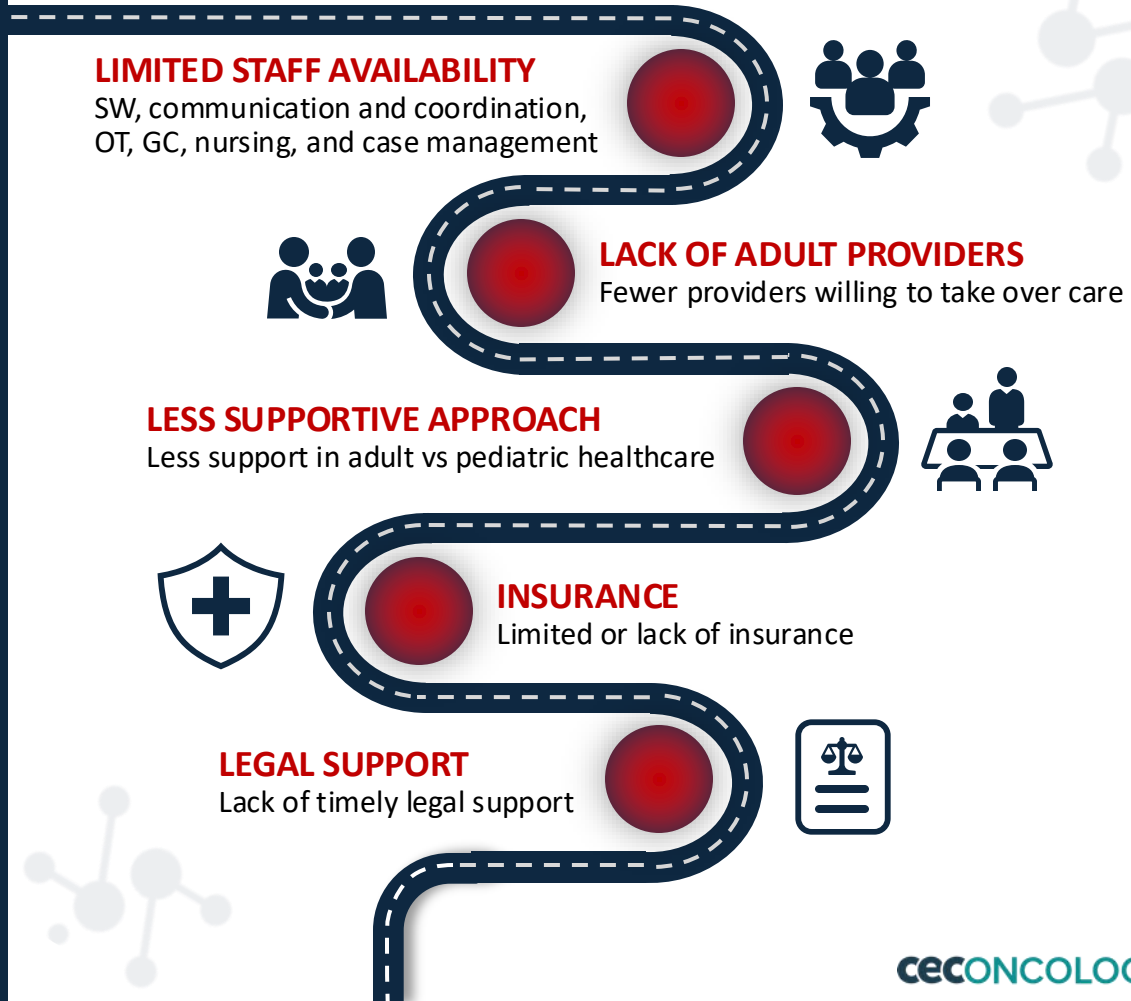
- Confirm transfer completion
- Elicit feedback

*Based on Dr. Hirbe's clinical experience and opinion.

White PH, et al. *Pediatrics*. 2018;142:e20182587.

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BARRIERS to Successful NF1 Health Care Transitions



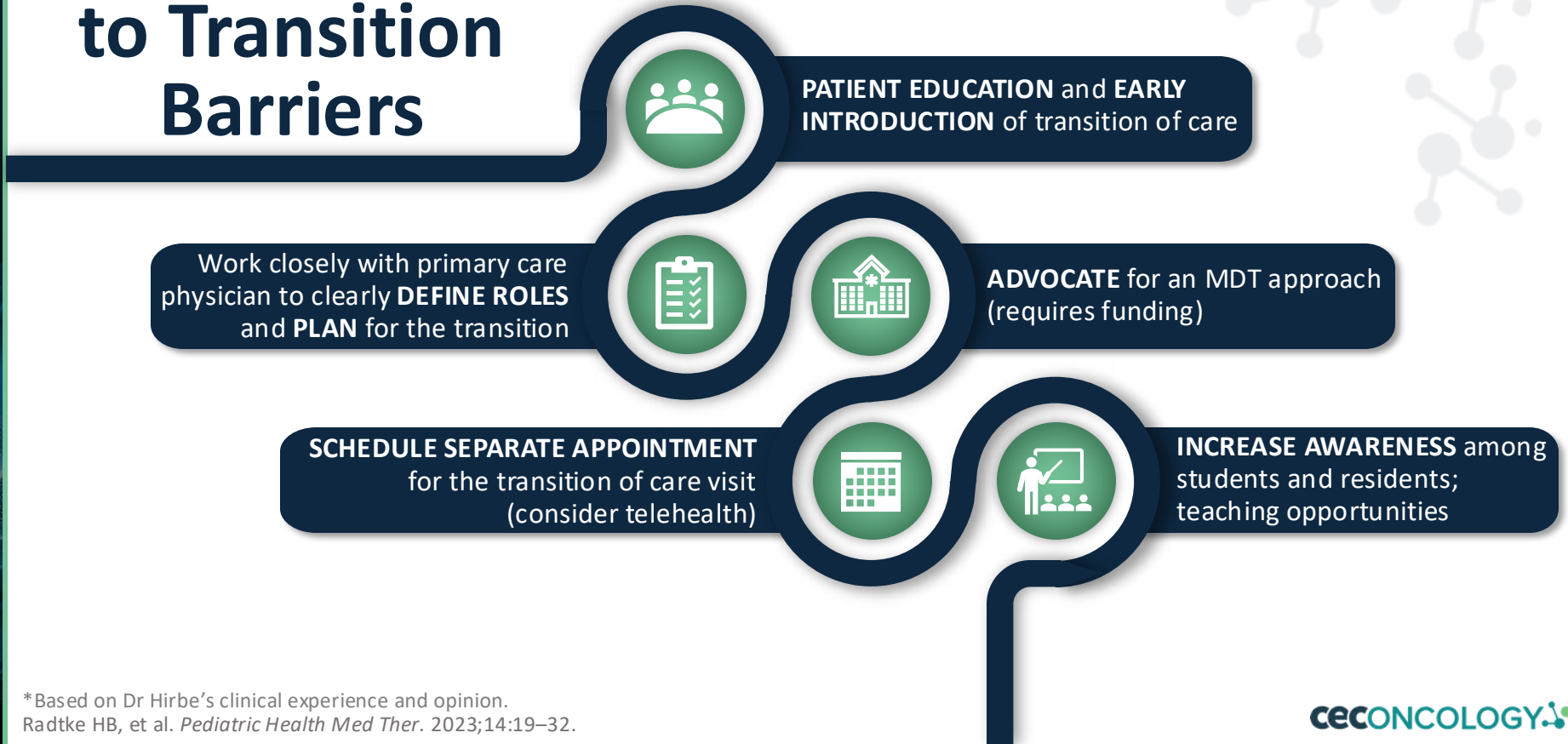
*Based on Dr Hirbe's clinical experience and opinion.

GC, genetic counselling; SW, social work.

Radtke HB, et al. *Pediatric Health Med Ther*. 2023;14:19–32.

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Potential SOLUTIONS to Transition Barriers



*Based on Dr Hirbe's clinical experience and opinion.

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/.

Summary

- 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
- 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/



Put information into action!

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

- *Develop a robust multidisciplinary team for NF1 patient care.* NF1 is a complex disease that requires support from many specialists. Clinicians should have a low threshold for calling in support from specialists in neurology, cardiology, nephrology, pulmonology, genetics, and other specialties.
- *Increase monitoring of patients on drug holiday.* Interruption of therapy may be possible for some patients but should be undertaken cautiously.
- *Implement strategies to improve transitions from pediatric care and integration into adult care.* Because patients with NF1 will need long-term care, clinicians and caregivers need to prepare adolescents to actively manage their disease, which may be challenging for a young person. Remember, it's not too early to plan for the future.

Additional Resources

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

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In-Person

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Claim ABIM MOC Credit

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

ABIM CME MOC ACCREDITED

CME for MIPS Improvement Activity

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

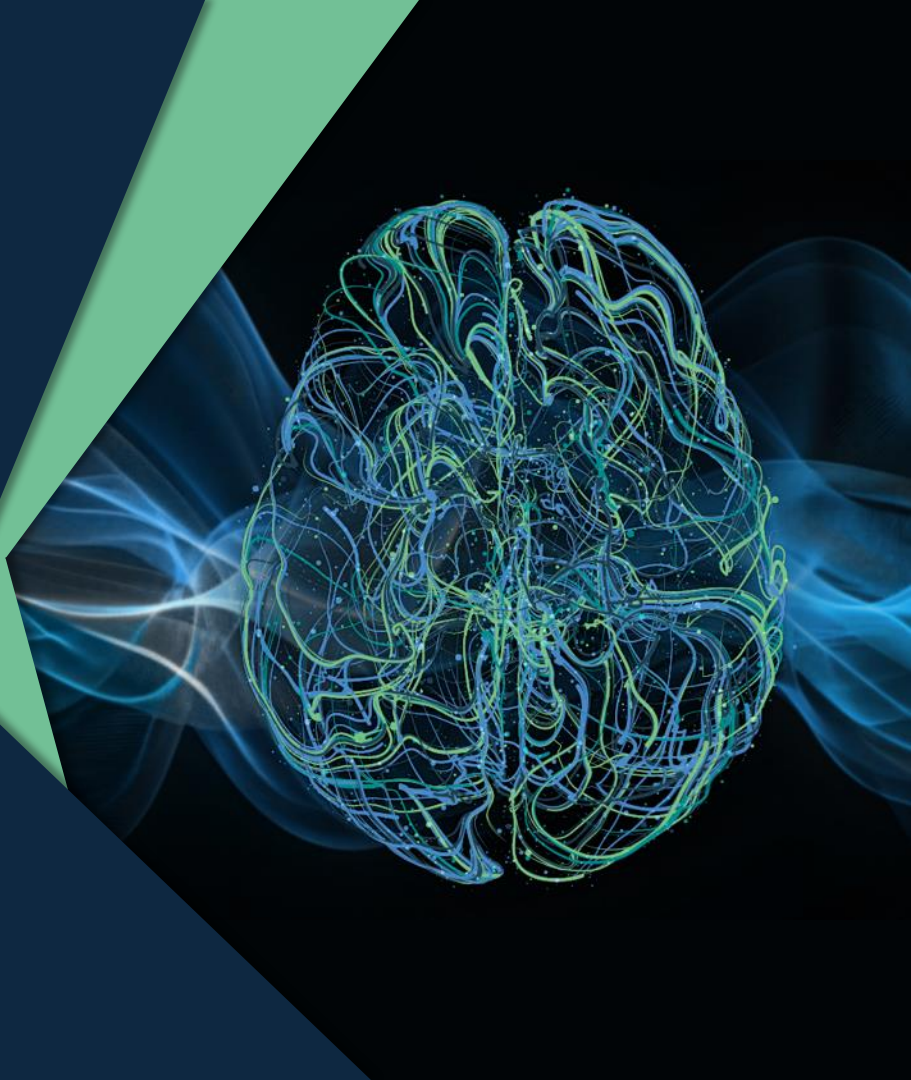
CME for MIPS IMPROVEMENT ACTIVITY

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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MEK INHIBITORS IN NEUROFIBROMATOSIS TYPE 1

LATEST ADVANCES AND REAL-WORLD APPLICATIONS IN NF1-PN MANAGEMENT



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