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Neurofibromas

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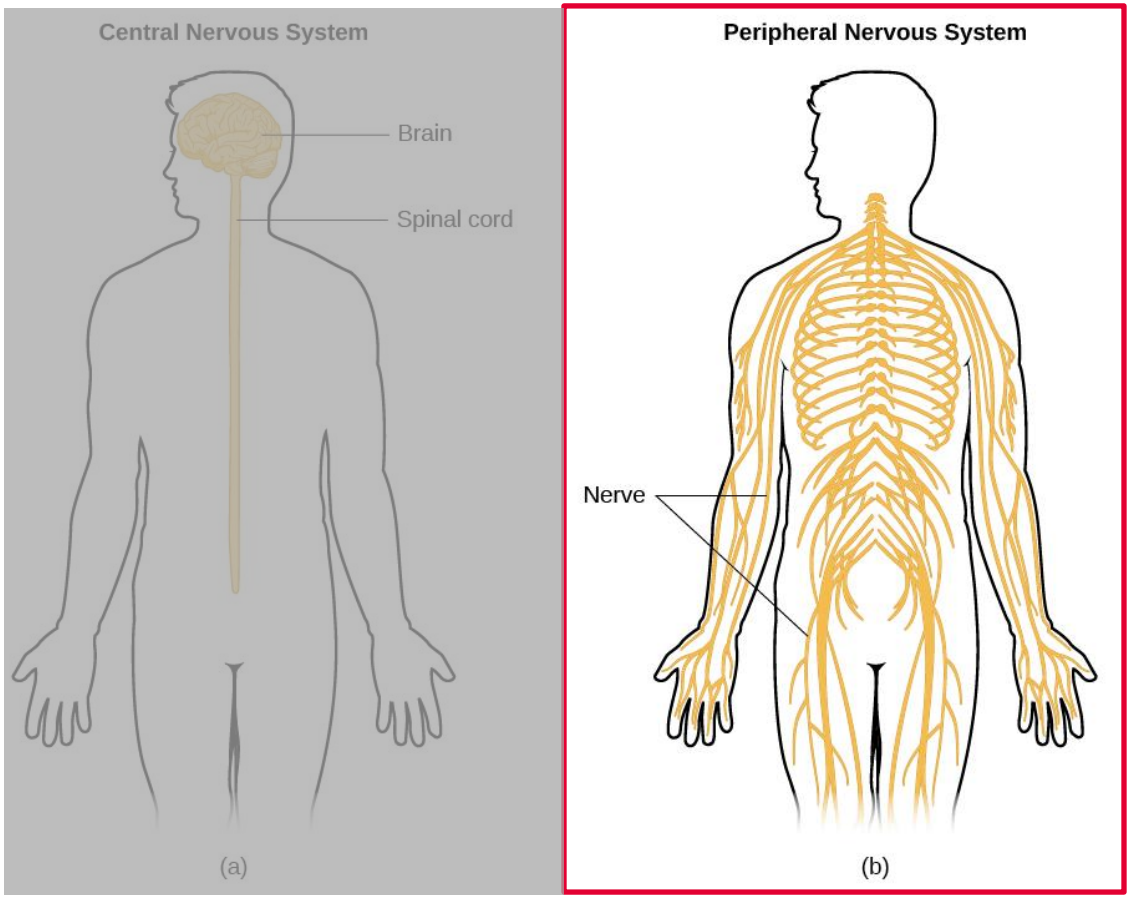
Outline

What is a neurofibroma?

Cutaneous Neurofibromas

Plexiform Neurofibromas

What is a neurofibroma?



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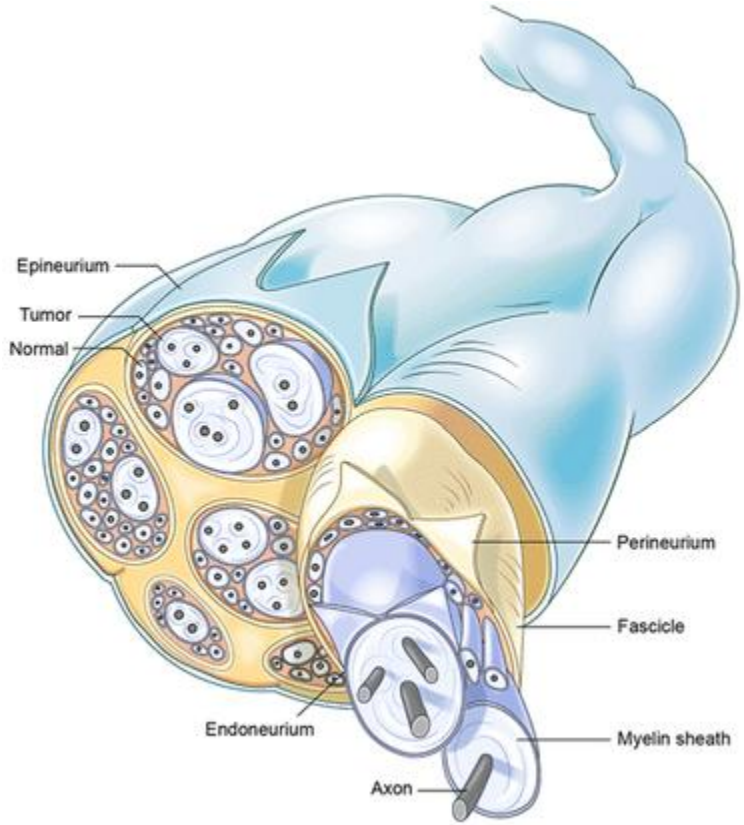
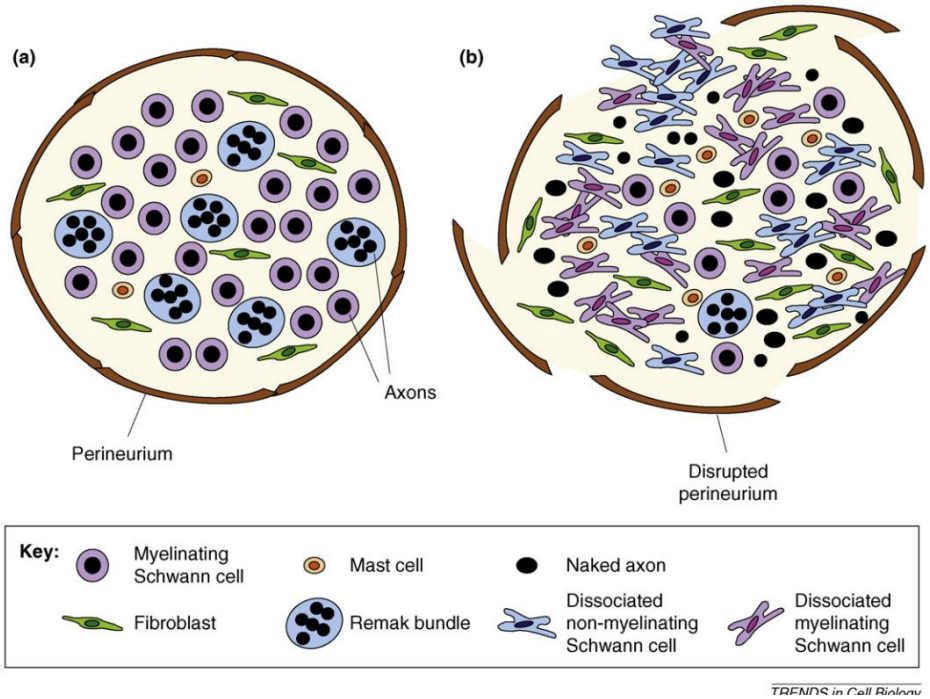
Source: LumenLearning.com

What is a neurofibroma?





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Source: Nelson et al 2019, Parrinello et al 2009

What is a neurofibroma?

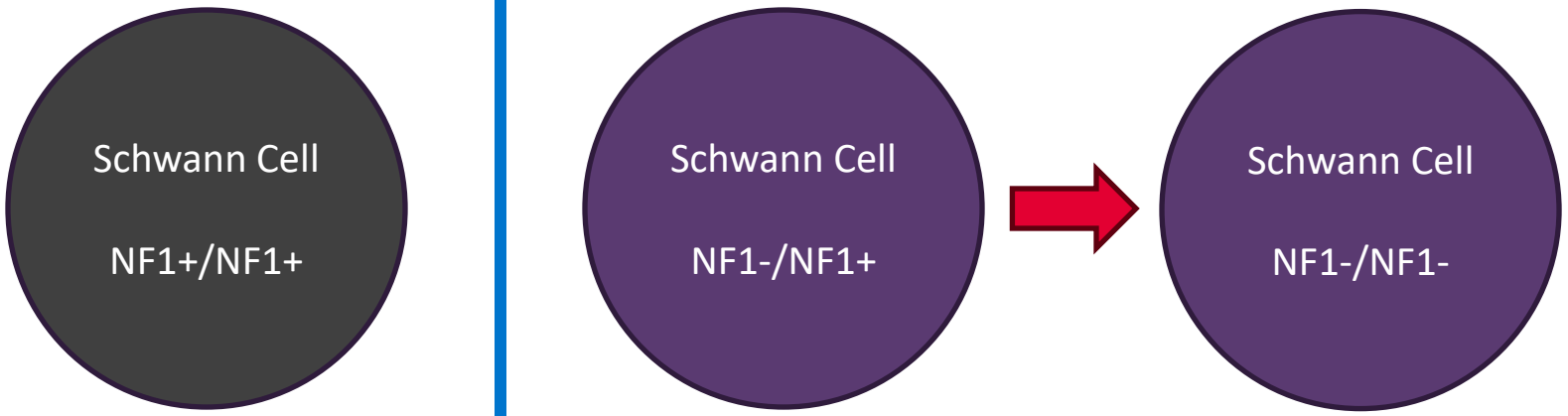
A benign tumor made up of nerve tissue along with other types of cells like mast cells, connective tissue cells, and blood vessels.

What does benign mean?

- Slow growth rate
- Does not invade or spread to other parts of the body

…But can still cause problems

Why neurofibromas in NF1



People without NF1

People with NF1

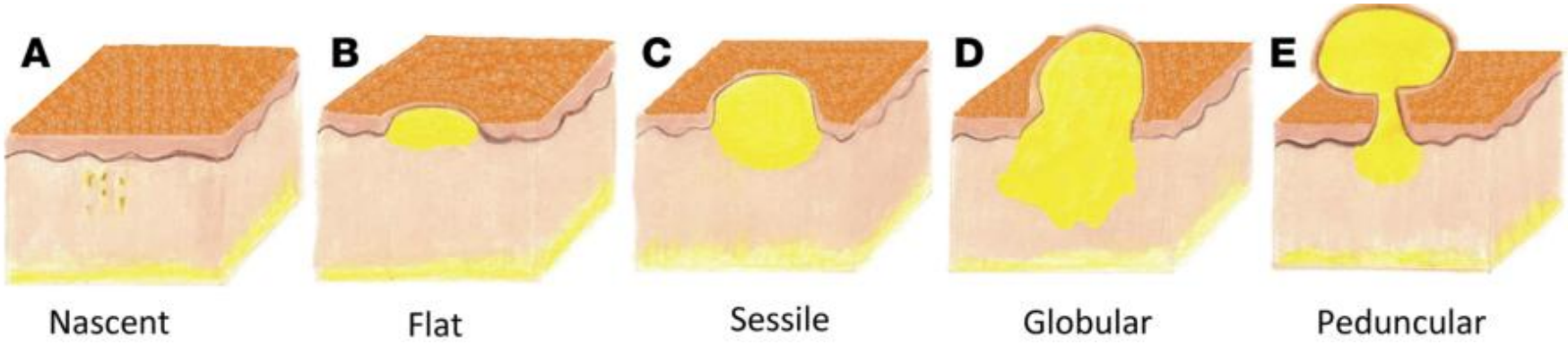
Types of Neurofibromas

Cutaneous neurofibromas

Plexiform neurofibromas

Cutaneous Neurofibromas

- Most common type of neurofibroma
- Develop along nerves on or under the skin
- Can have different appearances and textures



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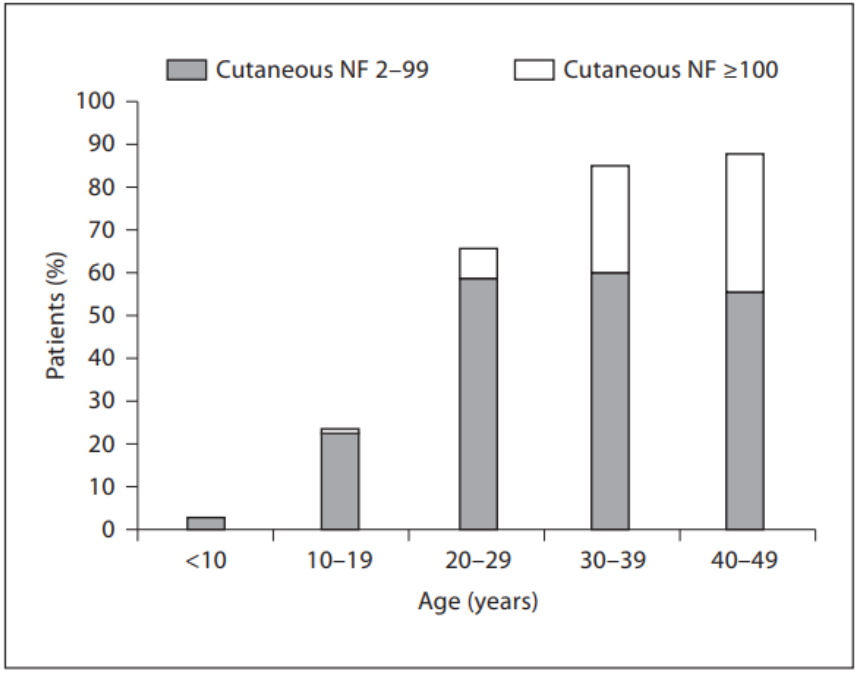
Source: Chamseddin et al 2019; CTF website

Who gets cutaneous neurofibromas?

- >90% of people with NF1 will have cNF by age 50
- Number of cNF increase with age, especially after puberty
- NF1 genotype does not usually predict number of cNF



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Source: Duong et al 2011

Are cNF harmful?

cNF do not become malignant/cancerous

But they can be bothersome

- Mast cells -> itching
- Catch on clothes
- Tender to the touch

Quality of life

79 individuals with NF1 completed the Skindex survey

The Skindex is a survey asking questions about how someone's skin condition affects their quality of life, for example:

- Pain level
- Sleep
- Social life
- Mood
- Itchiness
- Embarrassment

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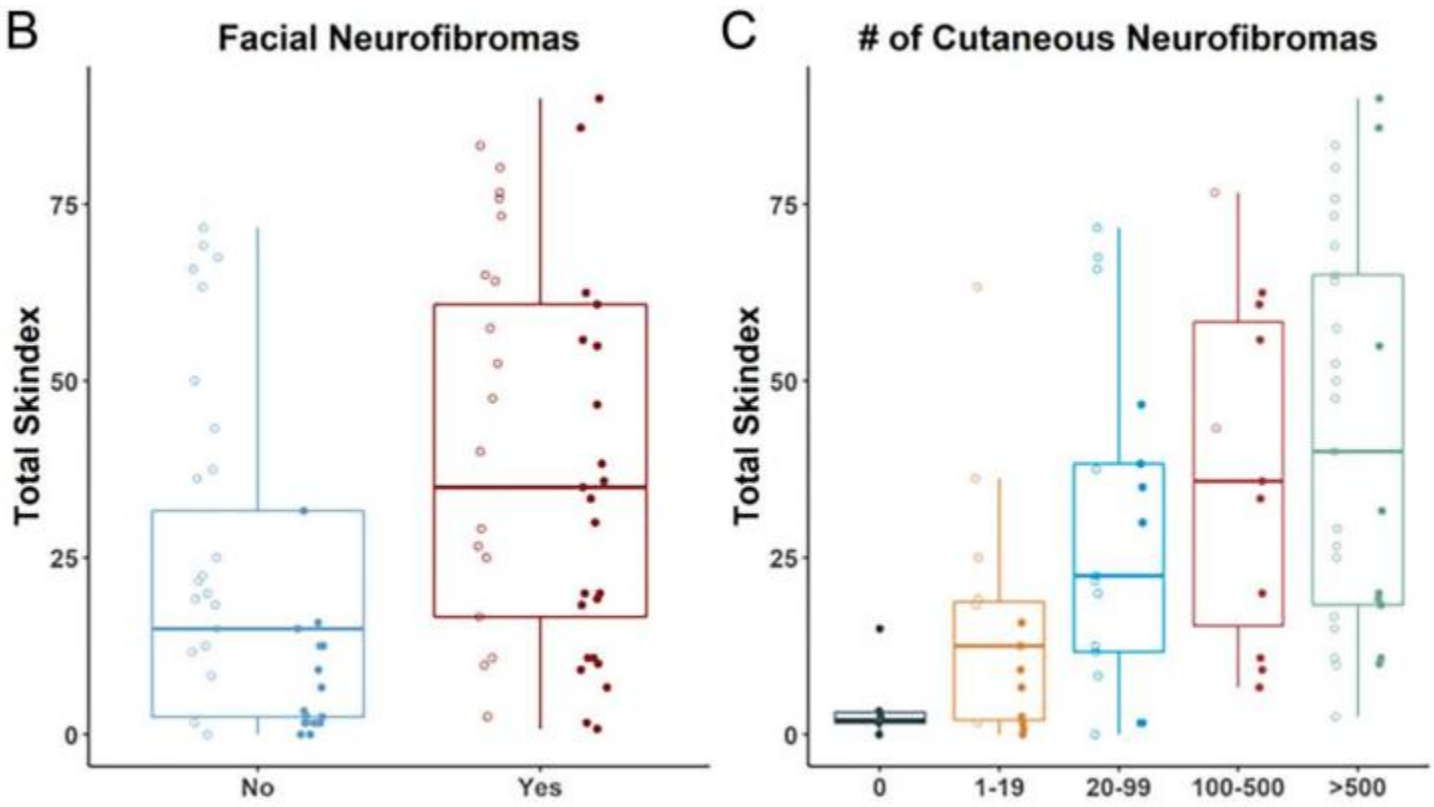
Source: Maguiness et al 2021

Quality of life



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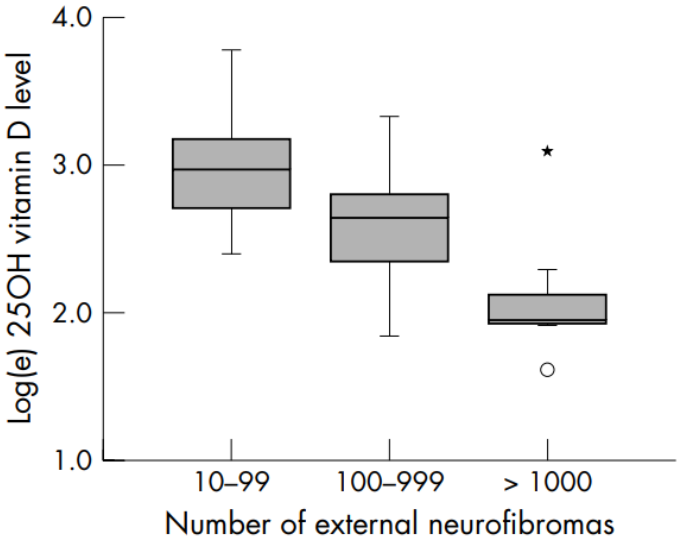
Source: Maguiness et al 2021

Cutaneous Neurofibromas and Vitamin D

Vitamin D helps the small intestine absorb calcium → bone health

Vitamin D level correlated with number of cNF



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Source: Lammert et al 2006

Treatment options

Symptomatic treatment
- Moisturizers
- Antihistamines for itching

Surgical removal – for larger neurofibromas

Other procedures: Laser, photocoagulation or electrodessication

Topical therapy

Clinical trial of 199 people with NF1 and cNFs for a topical anti-tumor medication nedometinib

- >18 yo
- At least 10 cNF

Participants were randomized to either placebo or 2 different concentrations of the study drug

Participants applied the gel once daily for 6 months

Primary objective: Percent of subjects with >50% reduction in cNF volume in 5 or more cNFs

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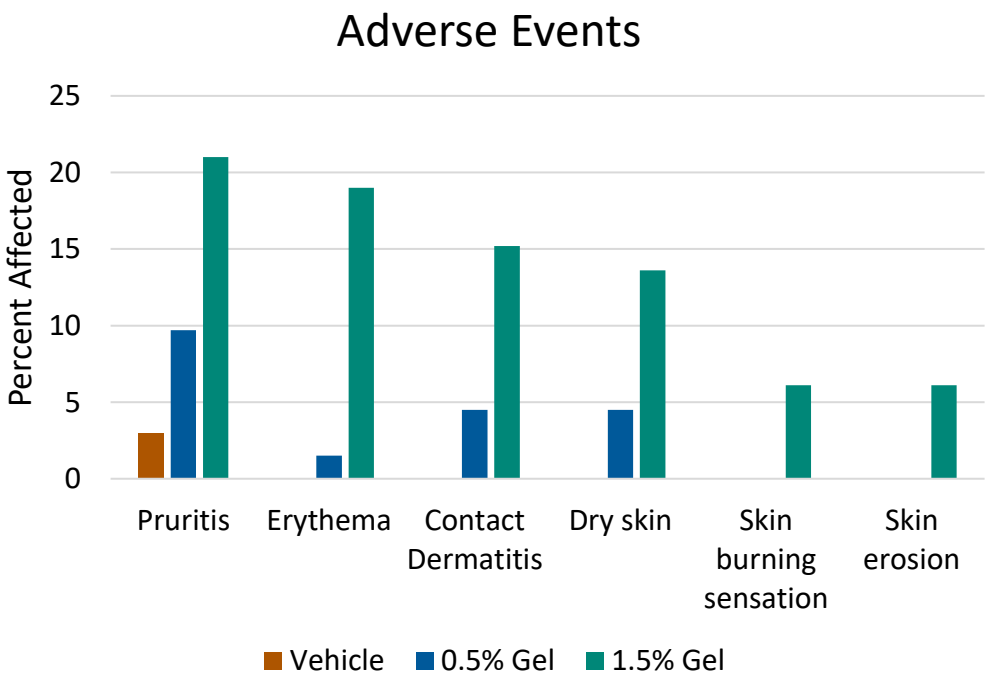
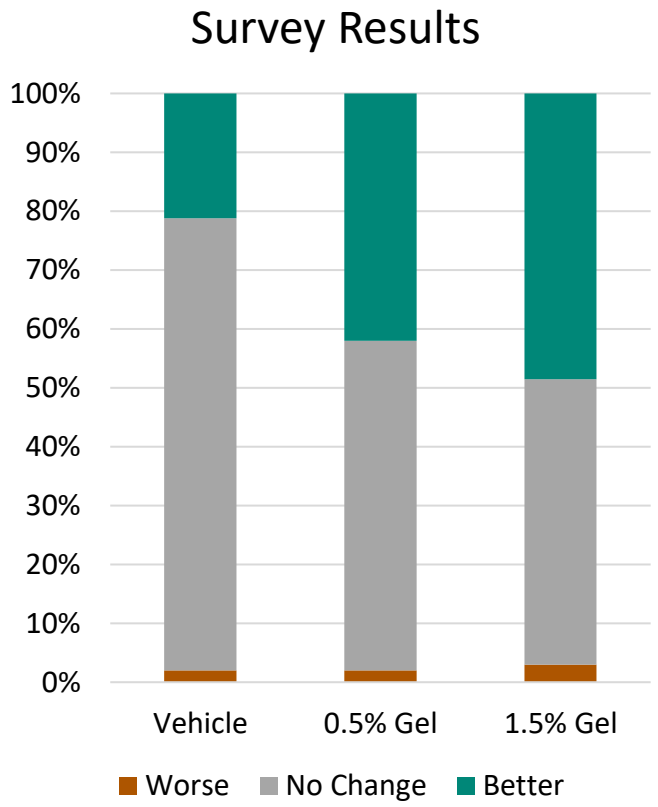
Source: Sarin 2024

Topical therapy, results

- Response observed in:
  - 24% for placebo
  - 34% for 0.5% concentration
  - 44% for 1.5% concentration





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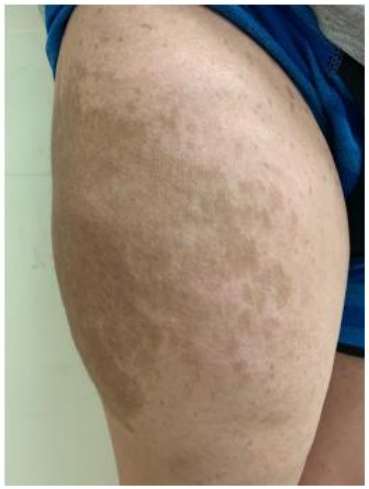
Source: Sarin 2024

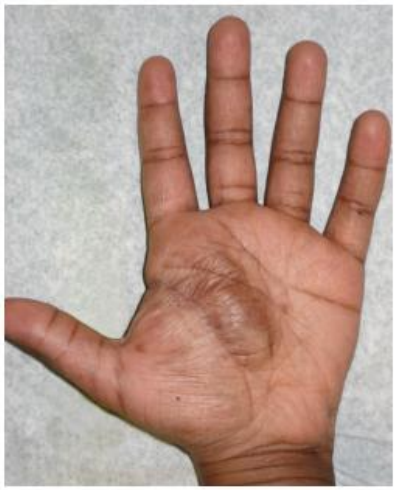
Plexiform Neurofibroma (PN)

Benign tumor that grows along peripheral nerve bundles

Compared to cNFs, PNs are often:

- Larger
- More diffuse with less well-defined borders
- Feel softer
- Present from birth and grow over time





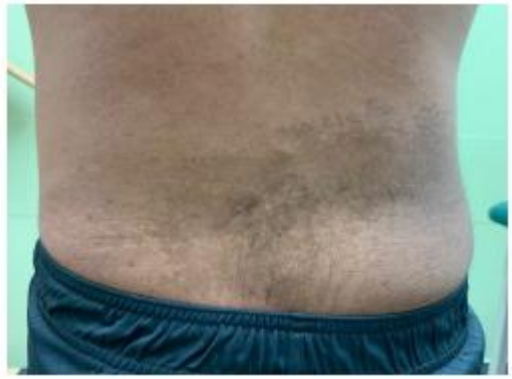


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Image source: CTF website

Who gets plexiform neurofibromas?

Thought to be present at birth

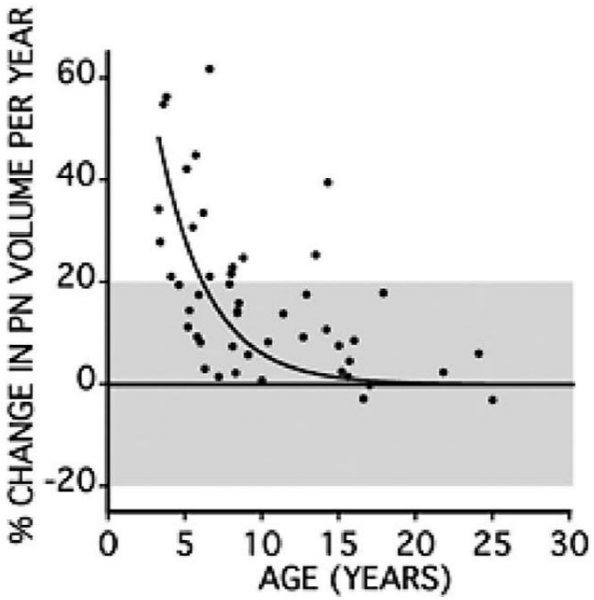
- But may be too small to see (even with MRI) or feel

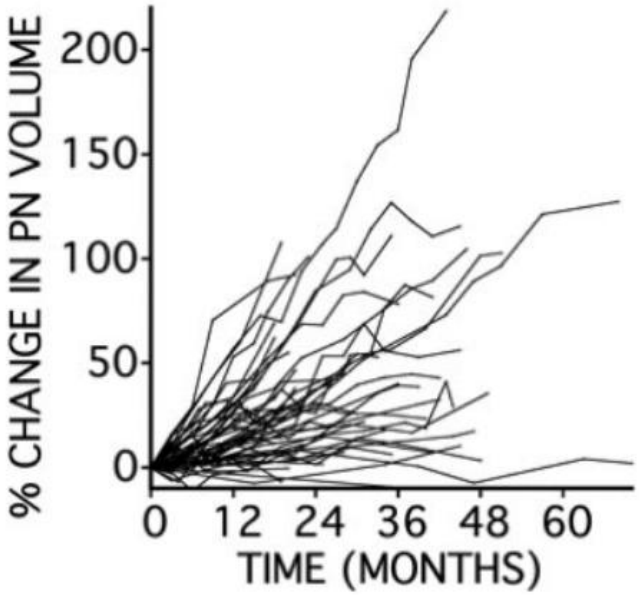
30-50% of people with NF1 will develop a PN

What happens to PNs over time?

Growth rate highly variable

Growth tends to slow down in adolescence





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Source: Dombi et al 2007

What are the risks of PNs?

Most commonly, do not cause symptoms

Disfigurement

Itching (because of presence of mast cells)

Depending on location, can cause problems due to mass effect

- Airway
- Bowel/bladder
- Vision
- Weakness
- Pain

PNs and malignant peripheral nerve sheath tumors (MPNSTs)

~10% of people with NF1 will develop an MPNST, which is an invasive and difficult-to-treat cancer

MPNSTs tend to come from pre-existing PNs, and people with a large volume of internal neurofibromas are at higher risk for MPNST

But, the **vast majority** of PNs never become cancerous

"Red flag" signs:

- Rapid growth
- Severe or persistent pain
- Change to firmer texture
- New weakness, numbness, tingling or bowel/bladder problems

Screening for Plexiform Neurofibromas

The American Association for Cancer Research recommends whole-body MRI post-puberty/prior to transition to adulthood (2024)

Why?

- If low tumor burden -> low risk of MPNST later in life
- Identify asymptomatic tumors, that should be monitored

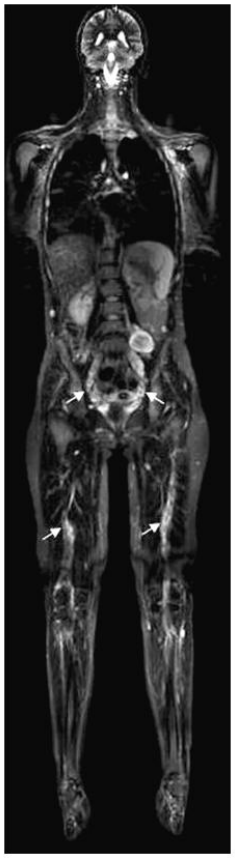

Image source: Mautner et al 2008
Perrino 2024

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When does a PN need to be treated?

Causing morbidity

Growing rapidly

Plexiform Neurofibroma Treatment

Surgery

- Prior to 2020, the only option
- Would be the optimal choice if tumor could be resected with out significant morbidity
    - Complete resection only feasible in ~15% of cases
    - Tumor regrowth and neurologic sequelae are common

Medical Treatment

Decision should be made with a multi-disciplinary team

PN Medical Treatment – MEK inhibitor

- NF1 protein acts as a "brake" on cell growth
- NF1 lost → overactivation of MEK → tumor growth
- MEK inhibitor drugs can slow tumor growth

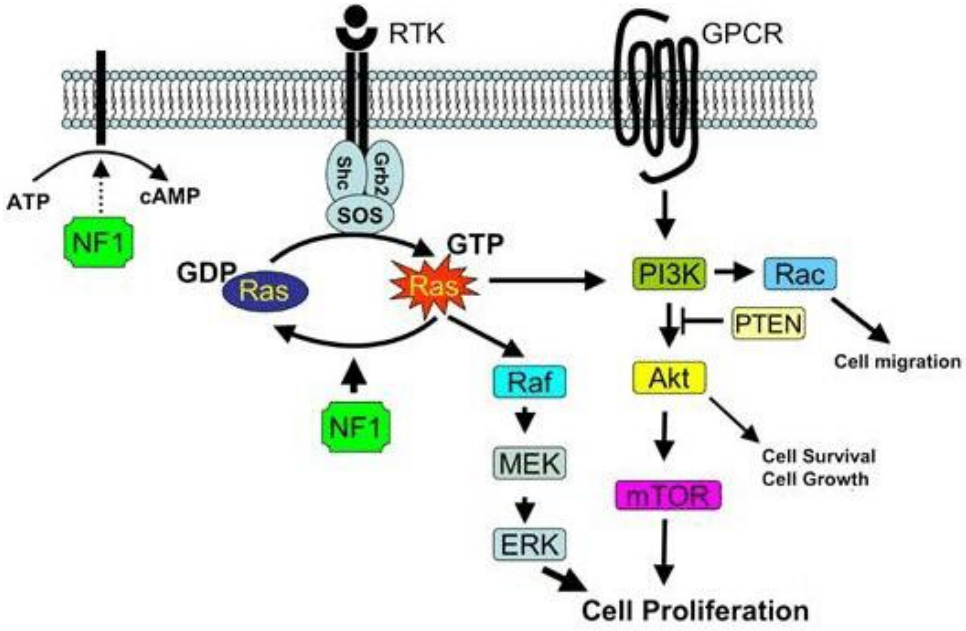

Image source: Lin et al 2019
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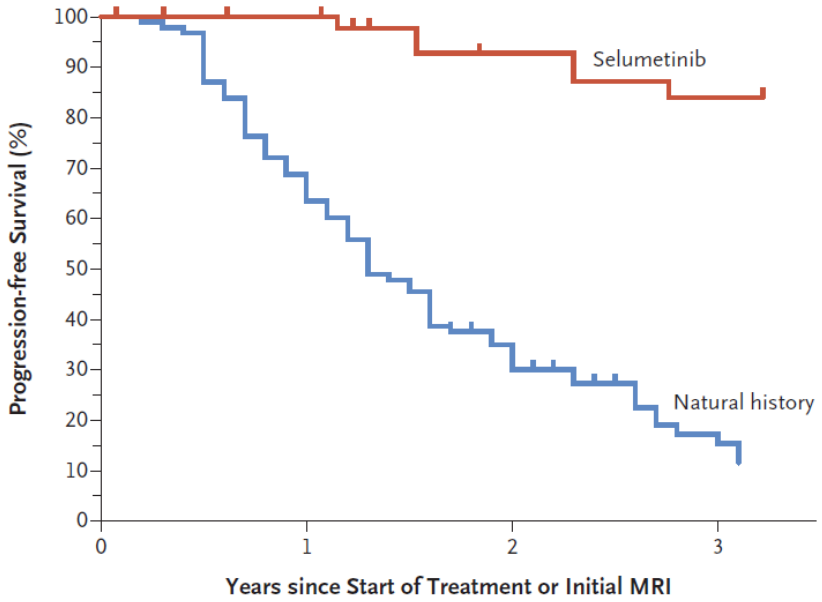
SPRINT Trial

Clinical trial of selumetinib in 50 children with NF1 and symptomatic, inoperable plexiform neurofibromas

Primary result: 33/50 (66%) had at least 20% reduction in tumor size



Adverse effects:

- Skin symptoms – rash, dry skin, acne, toe infection
- GI symptoms – diarrhea, nausea, weight changes
- Hair thinning or color change
- Cardiac function
- Eye toxicity

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Source: Gross et al 2020

Other treatment options in the pipeline

Other MEK inhibitors
- Mirdametinib
- Trametinib
- Binimetinib

Non-MEK inhibitor
- Cabozantinib
- Nitroxoline

Combination approaches

What about prevention?

Opening soon at CNH:
Phase 2 Trial of Selumetinib for the Prevention of Plexiform Neurofibroma Growth and Morbidity in Neurofibromatosis Type 1

Main question: **In children with asymptomatic plexiform neurofibromas, can we prevent growth and tumor symptoms with MEK inhibitor treatment?**

Eligibility:
- Children 1-8 yo with NF1
- No known plexiform neurofibroma

Study Plan
- Whole body MRI at study enrollment
- If high-risk PN is identified -> randomize to selumetinib or observation

Key Points

Cutaneous Neurofibromas

- Present in >90% of people with NF1
- Increase in number with age
- Not physically harmful but can be uncomfortable or psychologically distressing

Plexiform neurofibromas

- Present in 30-50% of people with NF1
- Thought to be present at birth, increase in size through adolescence, then usually stabilize in adulthood
- Usually asymptomatic but can cause pain or disfigurement
- Treatment options: Surgery, MEK inihibtors

References

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Questions