Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

- If sharing any data or information from these slides generated by the REiNS International Collaboration, please acknowledge the authors, group chairs, and specific working group.
- If using any information presented with a citation, please reference the primary source.

Neurofibromatosis
Therapeutic Acceleration Program
at Johns Hopkins

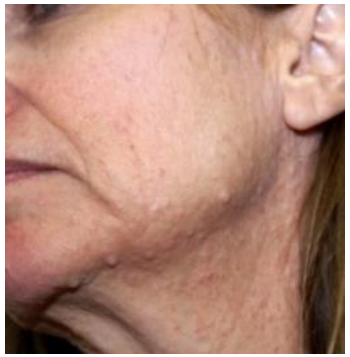
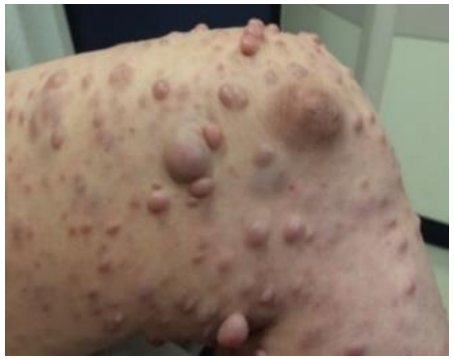
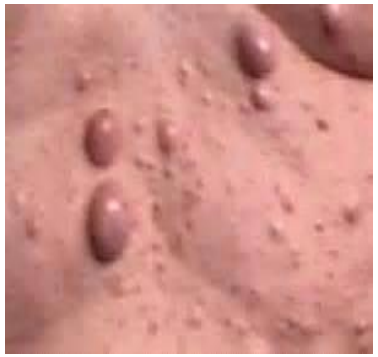
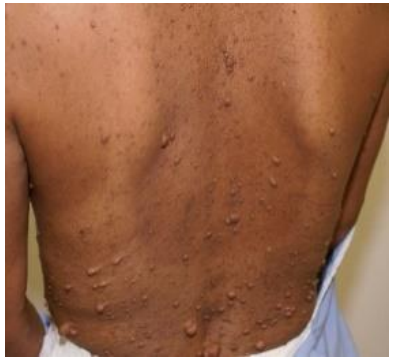
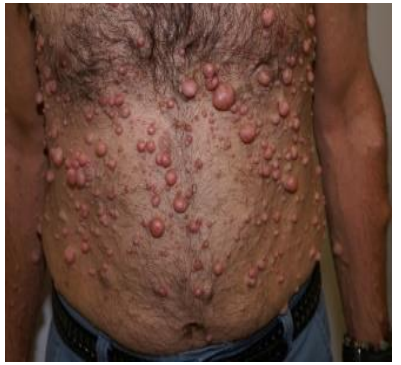
NATURAL HISTORY STUDY OF CUTANEOUS NEUROFIBROMAS IN PEOPLE WITH NF1

DECEMBER 5, 2022

VECTRA WB360 3D imaging system captures entire exposed body in single capture.

CUTANEOUS NEUROFIBROMAS (CNF)

- Present in >95% of adults NF1
- Significant effects on quality of life
- Increasing patient feedback about priority
- Unique biology, distinct natural history from plexiform neurofibromas

"The number continues to grow and grow… no end."

"They all bother me. Every thing about this stupid NF1 bothers me. I work third shift so I don't have to see a lot of people."

"Sometimes it's difficult to deal with the stares. It's not just one fibroma but many that invite the stares."

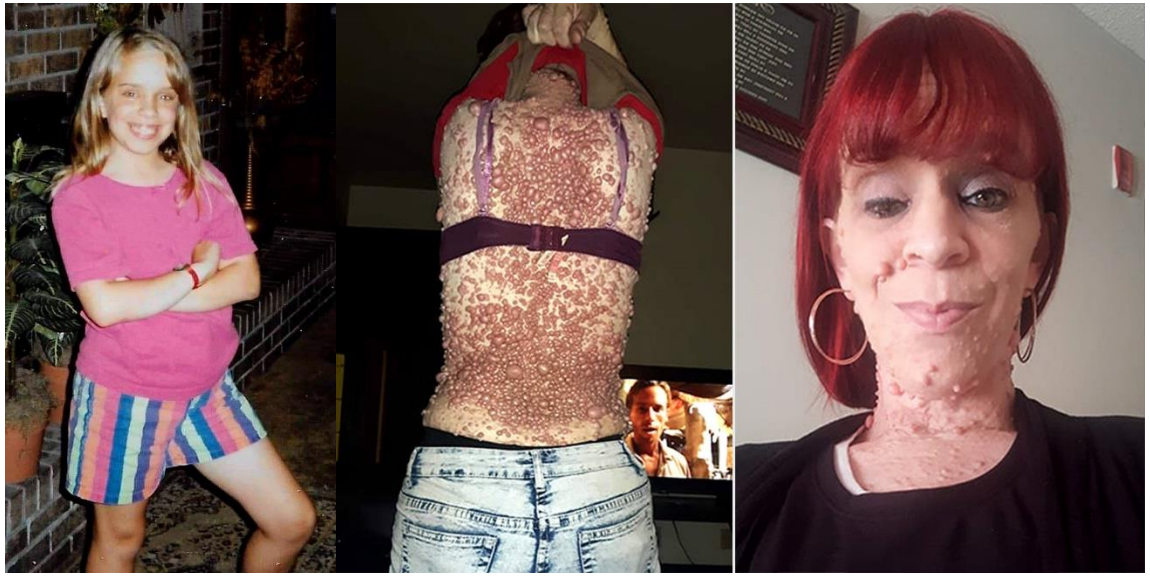
"I look and feel like a monster;" "I feel like a genetic freak."

NTAP

Huson S, et al, Brain, 1988
Wolkenstein P, Arch Dermatology, 2001
Granstrom S, et al., Dermatology, 2012

CUTANEOUS NEUROFIBROMAS (CNF)

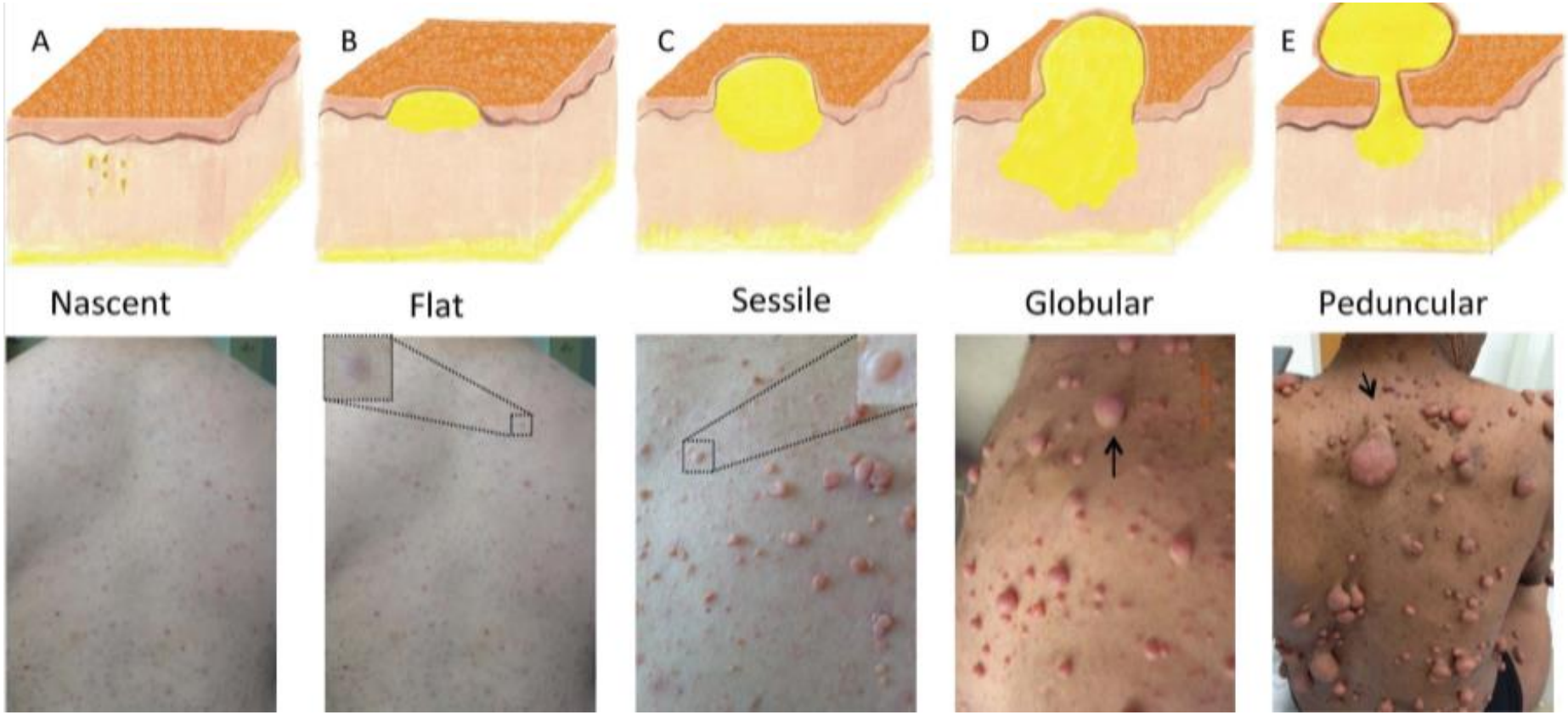
- There are no known ways to prevent cNFs from developing or progressing.
- Current treatments are limited to local or regional procedures.
- Condition is progressive over years, from minimal visibility to significant disfigurement.



People Magazine, By Morgan Smith January 15, 2020 12:40 PM

Pictures from the Daily Mail UK. PUBLISHED: 07:09 EDT, 12 May 2017 and April 7, 2019

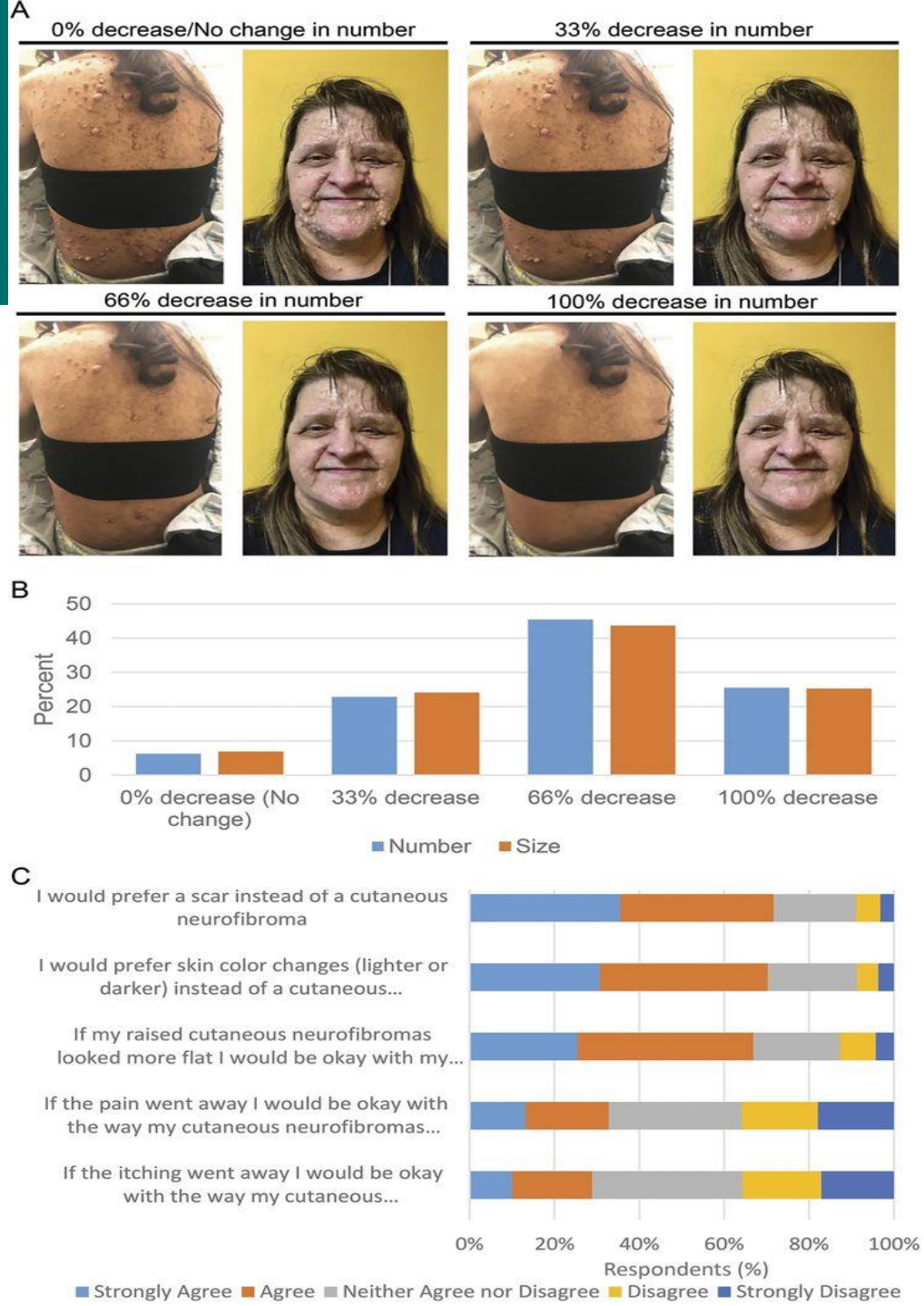
WORKING CLINICAL DEFINITION OF CNF



Chamseddin et al, JCI Insight., 2019
Ortonne et al., Neurology., 2018

KEEPING THE GOALS OF CLINICAL APPLICATIONS IN MIND

- Established cNFs: reverse disfigurement in an area
  - 75% of 548 adults with NF1 reported that a partial decrease of 33-66% in number ***or*** size of cNFs as meaningful.
- Early cNFs: prevent development or progression of cNF to prevent disfigurement
- Treatments will be needed over long periods of time and prevention will need to start early in life (children, adolescents)
  - Must be very tolerable, negligible side effects or require only intermittent treatment

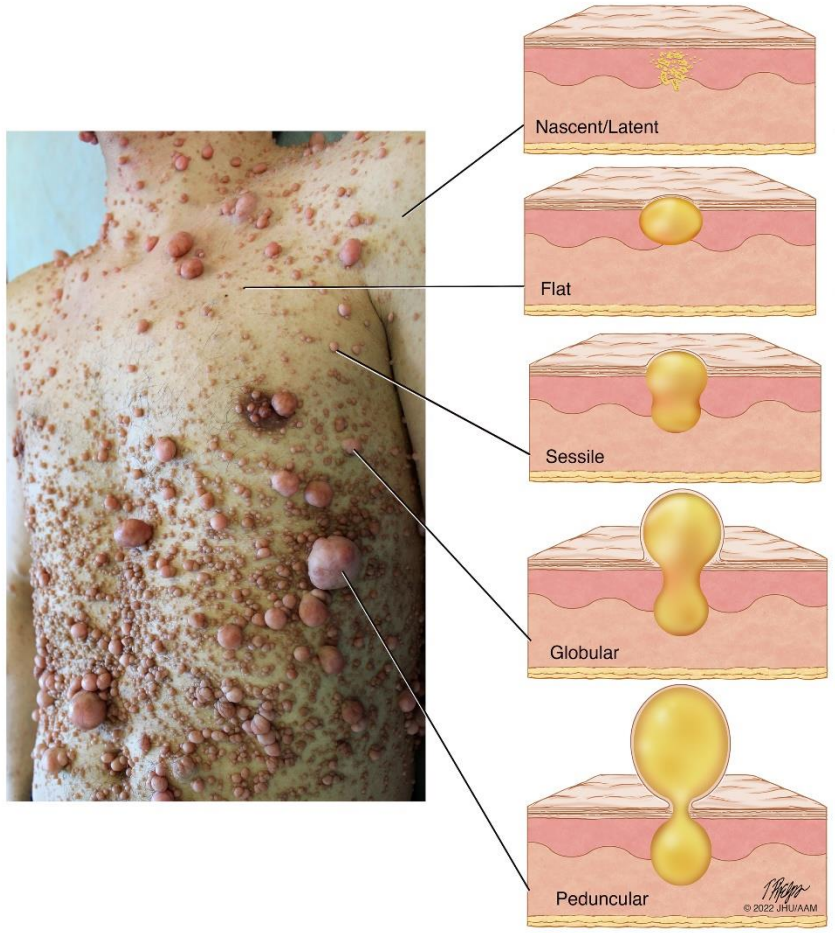


Cannon A, et al., REiNS International Collaboration. Perspective of Adults With Neurofibromatosis 1 and Cutaneous Neurofibromas: Implications for Clinical Trials. Neurology. 2021 Aug 17;97(7 Suppl 1):S15-S24.

NTAP

INFORMING CLINICAL TRIALS FOR CNF

- Multiple challenges hinder clinical trials:
  1. Incomplete natural history: precludes **identification of population at risk**
  2. Manual counting or measuring of cNFs: labor-intensive, **not always accurate or feasible**
  3. **Lack of clearly defined endpoints** in clinical trials to assess response



NTAP

NATURAL HISTORY STUDY OF CUTANEOUS NEUROFIBROMAS IN PEOPLE WITH NF1: AIMS

- **Aim 1.** Accrue a cohort of 20-30 people with NF1 and at least one cNF to assess the feasibility, as defined by accuracy, reproducibility and time burden, of using WB360 - 3D whole body imaging system to quantify cNF.
  - **1a.** Assess the reliability of using 3D whole body (WH) photography to quantify cNF (≥4 mm) burden across different age groups and skin types.
  - **1b.** Compare the time efficiency of digital counting on 3D whole body photography with that of manual counting.
  - **1c.** Assess a clinician's semi-quantitative categorization of tumor count vs count by 3D whole body photography at baseline exam (severity scale).

NTAP

NATURAL HISTORY STUDY OF CUTANEOUS NEUROFIBROMAS IN PEOPLE WITH NF1: AIMS

- **Aim 2.** Evaluate the natural history of cNF across age groups and evaluate the relationship between tumor burden and patient reported symptoms and quality of life.
  - **2a.** Baseline characterization of tumor burden by age group.
  - **2b.** Evaluation of changes in cNF number of cNFs over five years in a large cohort of patients from all ages (n=500) divided in 5 groups by age group (<10, 10-19, 20-39, 40-50, >50 years).
- **Aim 3.** Characterize the landscape of *NF1* variants and evaluate potential relations between genotype and phenotype – Invitae saliva testing.
- **Aim 4:** Explore a relation between cNF burden (defined as high (>50), moderate (10-50), or low (<10)) and patient reported outcomes tool (modified Skindex) and PedsQL questionnaires.

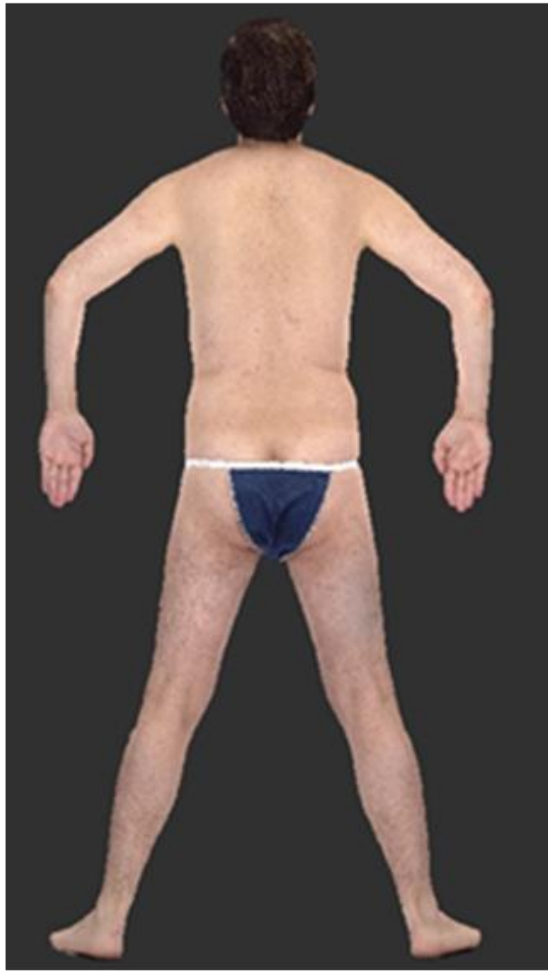
NTAP

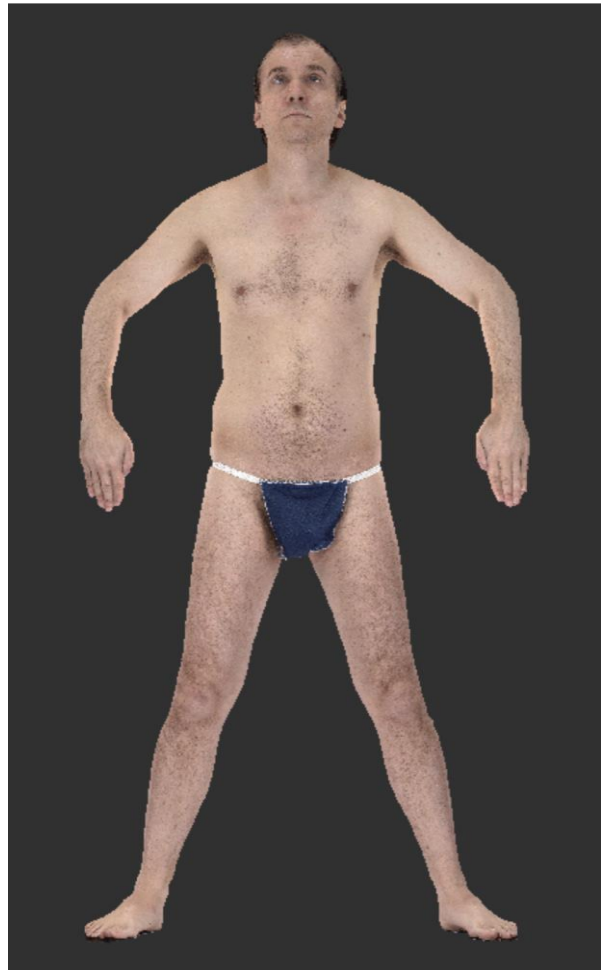
NATURAL HISTORY STUDY OF CUTANEOUS NEUROFIBROMAS IN PEOPLE WITH NF1: AIMS

- **Aim 5:** Store blood and cNF tissue samples in the existing biobank (Johns Hopkins IRB-approved biobank, "A Nerve Sheath Tumor Bank from Patients with NF1" - IRB 00096544) through optional donation at any point during the study, but ideally at enrollment and during yearly follow up appointments, to coincide with phenotypic evaluation, for future biomarker discovery.

NTAP

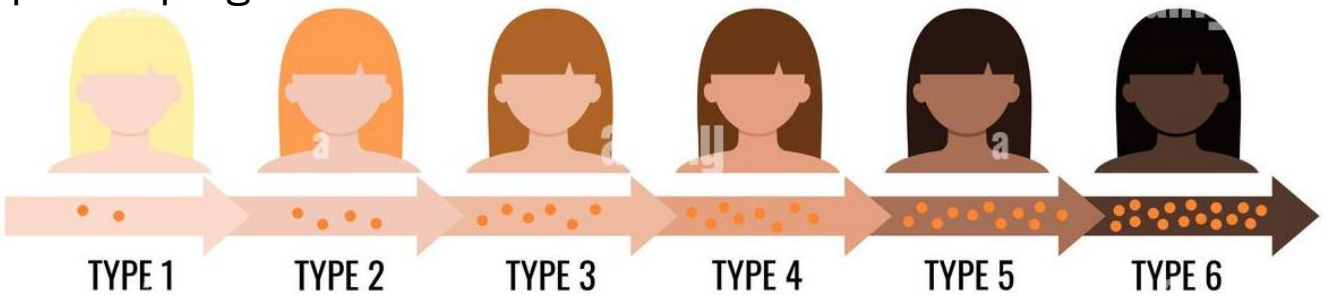
VECTRA WB360 CAMERA AND DIGITAL IMAGES





CNF NATURAL HISTORY OVERALL DESIGN

- N=500 people with NF1
- All skin phototypes, all severity of cNF (none to high burden)
- Demographic data collected at baseline (patient reported):
  - Age at enrollment, age at NF1 diagnosis, age at cNF onset, sex, race, ethnicity, education status, Fitzpatrick skin phototype, treatment history for any NF1 indication, hormonal therapies or pregnancy
- Baseline and annual evaluations:
  - WB digital images: VECTRA WB360 3D imaging system (Canfield Scientific) annually
  - PROs (cNF Skindex and PedsQL: QoL inventory and NF module)
  - Physician global impression of change
  - cNF treatments
  - Hormonal therapies or pregnancies



Study Shema:

Initial cohort:

Patient who meets NIH clinical criteria for NF1 or has a pathogenic *NF1* mutation

→ 1. Eligibility screening 2. Informed consent

→ **Validation cohort:**

Baseline:

- Whole-body imaging w digital count twice from two photographs taken on same day
- Skin exam with manual count of cNF
- Estimated count by clinician
- Completion of QoL tools (Skindex and PedsQL measures)
- Measure and record time needed to count cNF in-person and on 3D photograph

Next Generation sequencing of *NF1* gene*

→ **Evaluate:**

- Feasibility
- Reproducibility
- Time efficiency

Second cohort

Patient who meets NIH clinical criteria for NF1 or has a pathogenic *NF1* mutation

→ 1. Eligibility screening 2. Informed consent

→ **Grouping by age (years):**

<10	100 participants per group
10-19	
20-39	
40-50	
>50	

→ At baseline and yearly for up to 5 years:

- Whole-body imaging with digital count of cNF of whole back
- Skindex and PedsQoL questionnaires
- Physical examination
- Next Generation sequencing of *NF1* gene*
- Patient cNF severity scale
- Clinician cNF severity of scale (Global impression of change)

↓

Evaluate:

- Describe the distribution of tumor count by age group
- Estimate the rate of new tumors per year by age group
- Evaluate the ability of WB imaging to calculate the height of cNF in order to perform volumetric analysis
- Clinical validation of Skindex for cNF as a quality of life tool in this population and it is consistent with the severity score (mild, moderate or severe).
- Exploratory: Evaluation of genotype-phenotype associations with severity score. Based on 4 variant groups: 1. microdeletions, 2. stop codons and frame shift mutations, 3. Missense mutations and 4. Others

AIM 1: FEASIBILITY OF WB360 VECTRA IMAGING

Whole-body 3D photo #1

- Estimated count by clinician
- Clinician count of cNF on back (Timed)
- PROs
- Collection of saliva sample for *NF1* testing

Whole-body 3D photo #2

Clinician count of cNF in back on photos (x2)

Evaluation of:

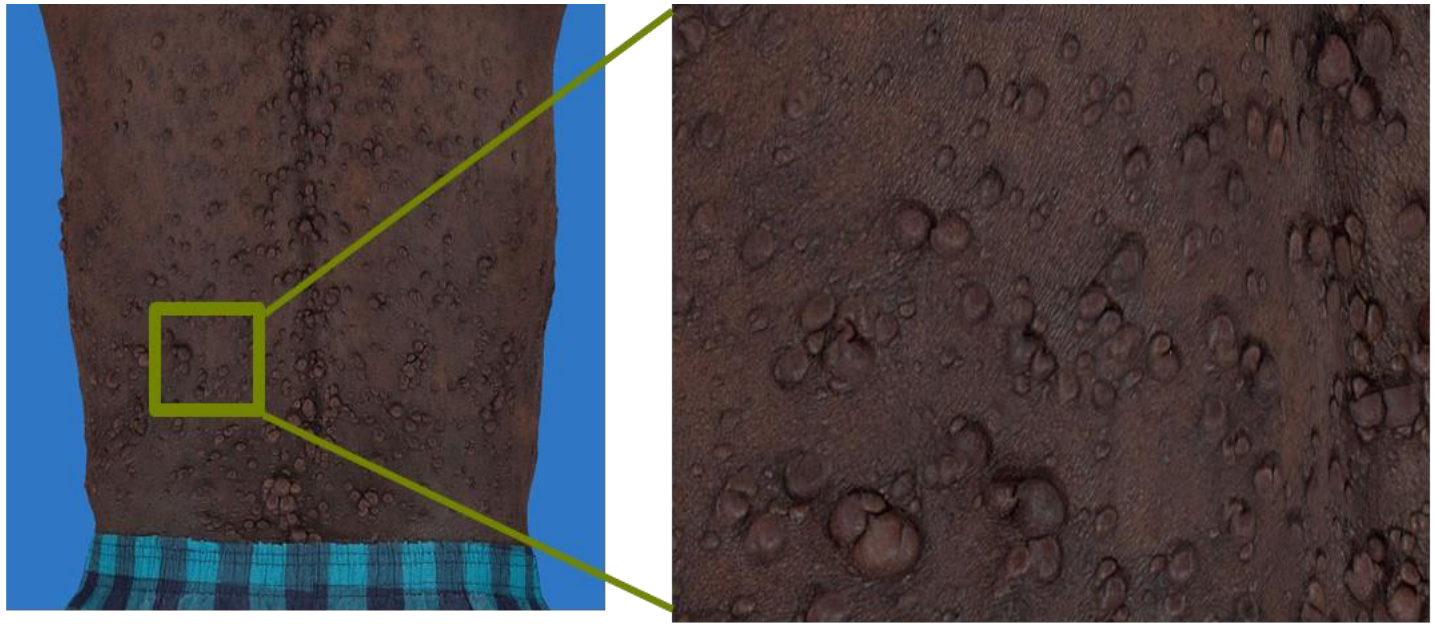
1. Feasibility
2. Reproducibility
3. Time required

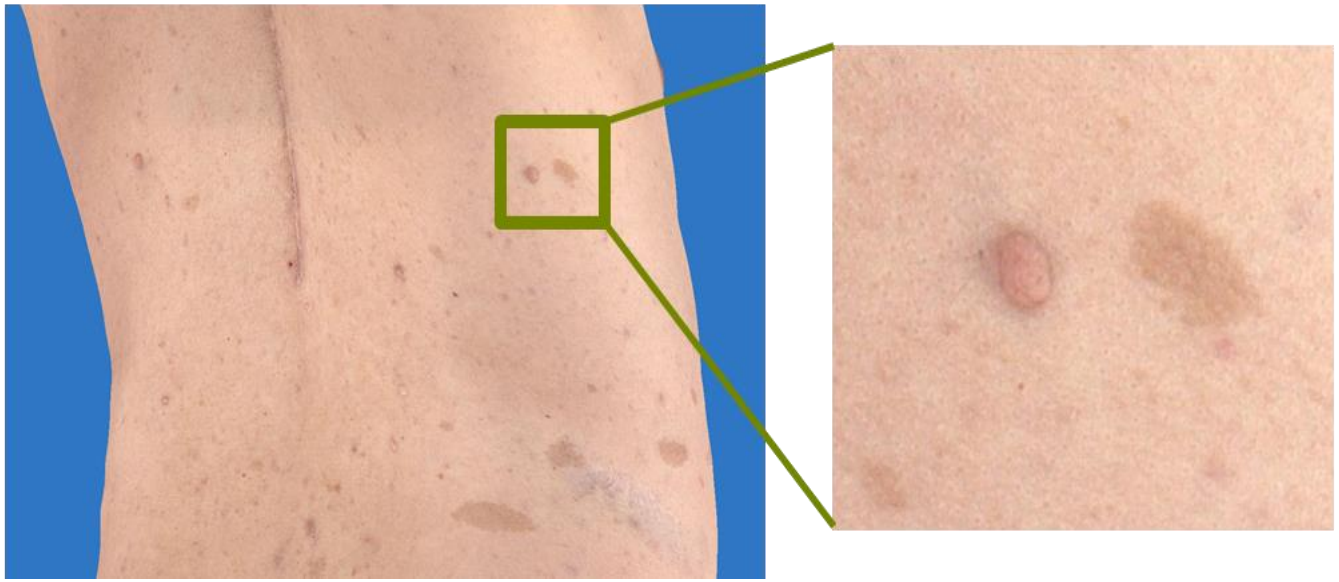
NTAP

RESULTS FROM AIM 1

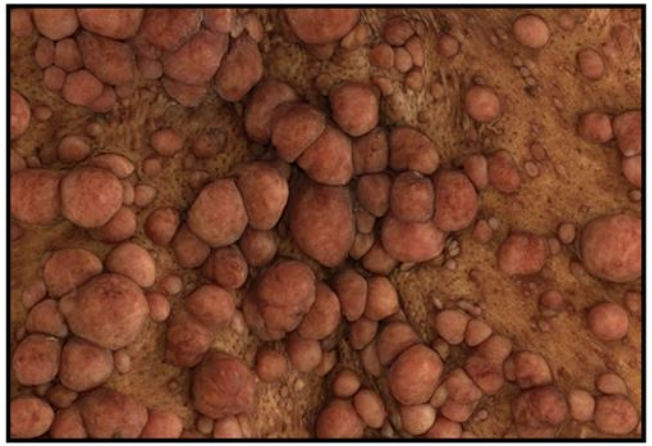
- N = 32
- Median age of patricipants: 24 years [range: 1 - 69]
- Female: 15 (47%); Male: 17 (53%)
- Fitzpatrick phototypes: I-VI
- Acquisition of high-quality images **was feasible** and cNFs were visualized well.
- Reproducibility: **100%** (0.9999, 95%CI:0.9998-0.9999, p-value=0.0001).
- Mean number of cNF:
  - 62 [range:0-1417] per in-person counting
  - 55 [range:0-1335] using imaging counting (p=0.92)
- Mean time:
  - In-person cNF count: **3.3 minutes** [range:1-50]
  - Count on photographs: **9.3 minutes** [range:1-186] (p=0.3).

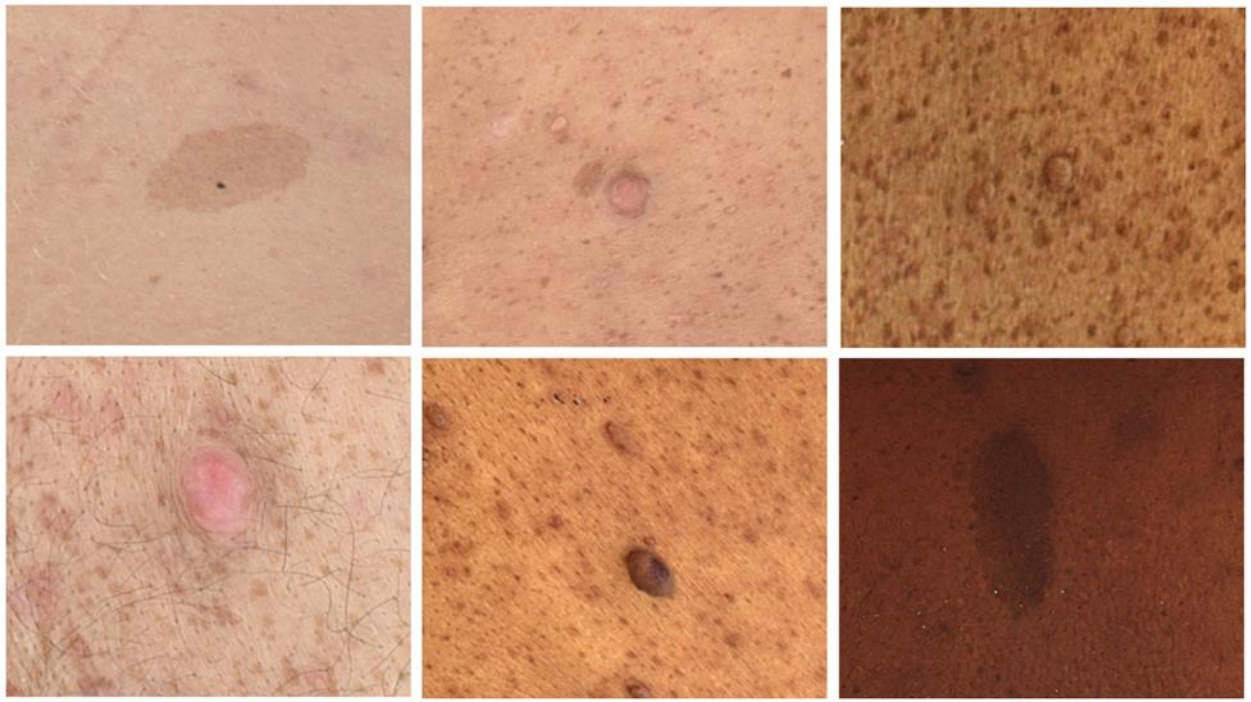
NTAP





NTAP





DATA ANALYSIS

Analysis Processes:

- Group participants by age
- Measure number and size of cNF tumors every 12 months
- Assess tumor growth trend over time using mixed regression model
- Logistic regression model to assess association of disease severity and Skindex for cNF
- Potentially use chi-square statistics to explore association between molecular subtype and cNF severity or QoL assessments
- Adjust analysis based on distribution of empirical data

Quantification of cNF (>4mm) burden

cNF burden (defined as high (>50, moderate (10-50), or low, (<10))

Evaluation of changes in cNF number of cNFs over five years

Germline NF1 variants

Patient reported outcome tools

NTAP

STATUS OF AIMS 2-5

- Enrollment:
  - N = 74/500 enrolled; 27 who have completed 1 and 2 year visits
    - 23 new participants recruited and will come in by Jan 31, 2023
- NF1 genetic analysis completion rate: 80%
  - 20% technical failure via sputum collection
- PRO completion: 100% (completed and reviewed in person at visit)

Age	%	Fitzpatrick skin type		Sex	
<10 years	11	I	4%	F	64%
10-19	16	II	34%	M	36%
20-39	27	III	19%		
40-49	14	IV	16%		
≥50	32	V	22%		
		VI	5%		

Travel: up to $700 if coming from outside of MD
Coordinated with clinical visits
$50 gift card

NTAP

SUMMARY AND FUTURE DIRECTIONS

- Novel therapeutic possibilities for cNF are available → urgency for identifying accurate mechanisms to assess cNFs.
- WB 3D digital imaging is feasible, reliable and provides durable source for documentation of cNF burden and change over time (progression or response to therapy).
- Improved automation techniques are required to detect and count cNF via digital images.
- Evaluation of the sensitivity to change over time and the natural history of cNFs will continue as a larger cohort (N=500) is recruited and monitored yearly for five years.

NTAP

ACKNOWLEDGEMENTS

- **Patients and their families**

- **NTAP Team**
  - Carlos Romo, MD
  - Christina Allen, PA
  - Joshua Roberts, PhD
  - Mandi Johnson
  - Jackie Eubanks-Rudd
  - Sang Lee, PhD
  - Rhonda Jackson
  - Karli Rosner, Md, PhD
  - Xiaobu Ye, MD, MS

- **Comprehensive NF Center at Johns Hopkins**
  - Bronwyn Slobogean, PA
  - Shannon Langmead
  - Verena Staedtke, MD, PhD

- **Department of Dermatology**
  - Sewon Kang, MD
  - Ruizhi Wang

NTAP