Measuring change in cutaneous neurofibroma size – novel techniques and endpoints

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Response Evaluation In Neurofibromatosis & Schwannomatosis

REiNS

Response Evaluation In Neurofibromatosis Schwannomatosis

INTERNATIONAL COLLABORATION

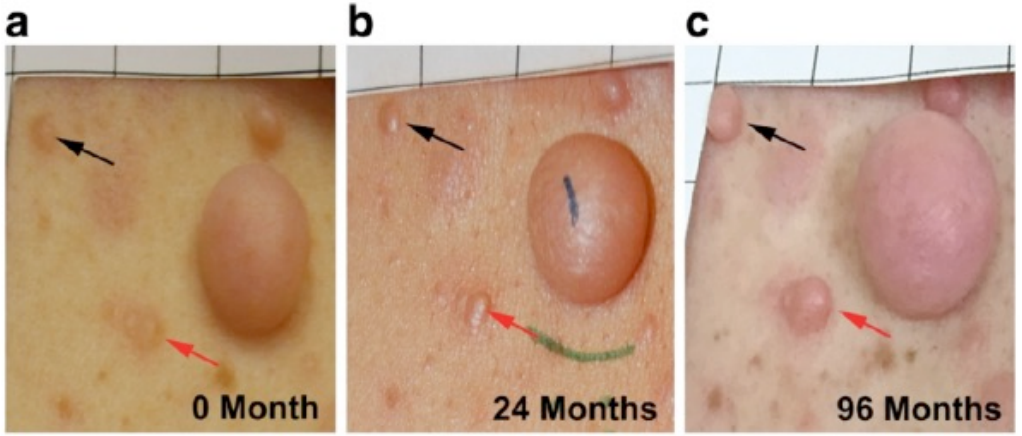
Disclosures

- Co-founder of NFlection Therapeutics

Background

- Currently, there are ***no known effective medical therapies*** to treat or prevent these lesions
- A major limitation to developing either novel interventions or drugs is the ***inability to assess intervention outcome*** with a reliable and reproducible measurement tool
- To date, the studies performed have relied on a variety of unvalidated measurement techniques for tumor assessment (caliper measures, physician assessment, and patient satisfaction assessments)

Clinical challenge:
How to measure very slow growth accurately

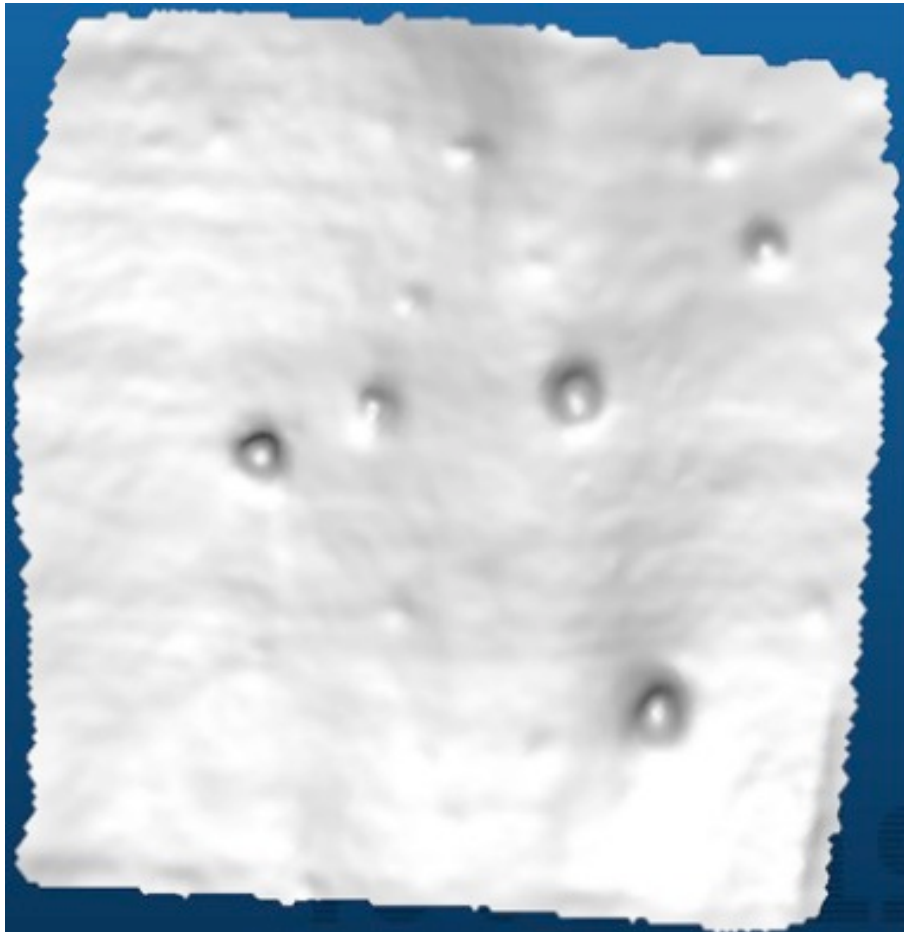


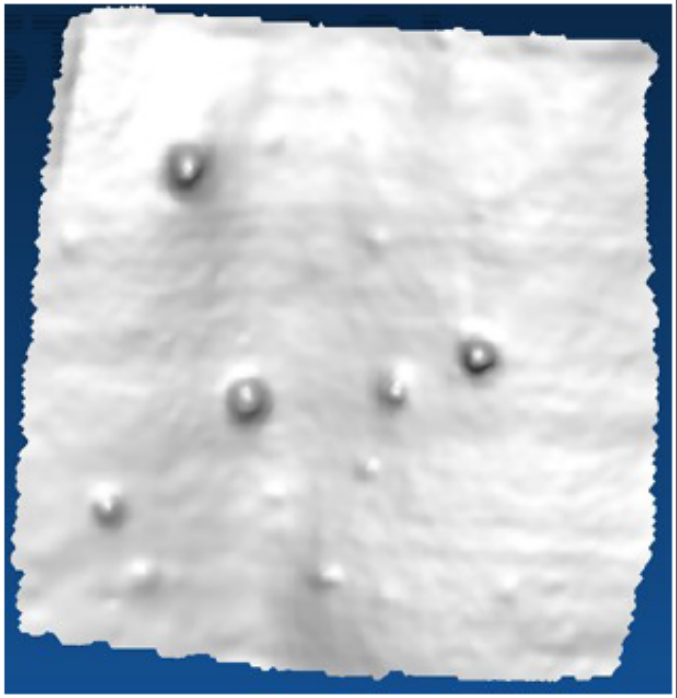
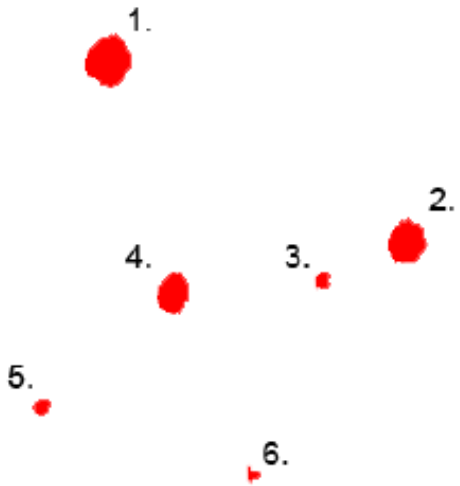
Cannon et al, 2018

FastScan laser scanner (2007)

- Currently, no technique to estimate tumor number

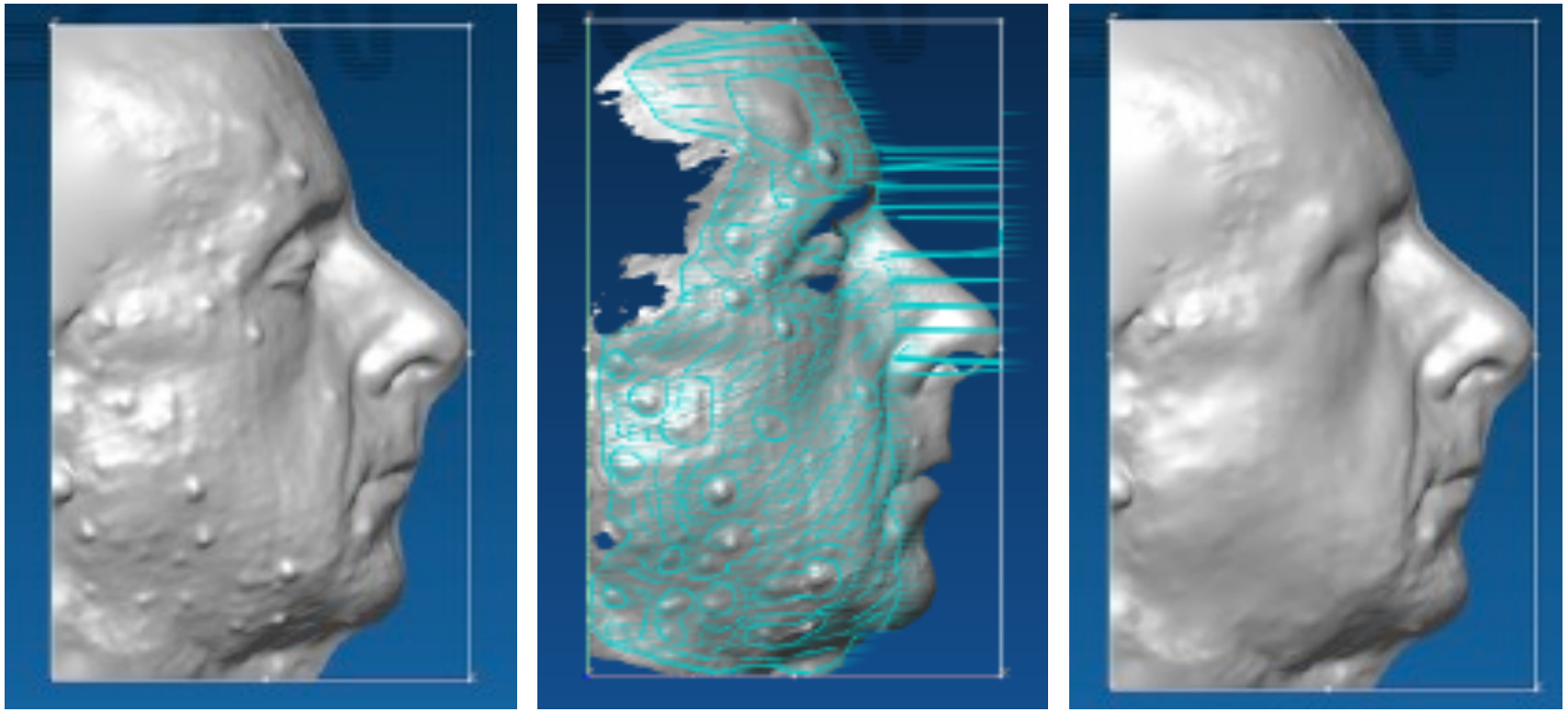
FastScan Laser Scanner



Actual Scan of the selected site on the back of subject S1	Tumor index Map used for measurements
	

	CO - SC	CO – BP	SP - SC	SP - BP	SR – SC	SR – BP	Variability	Average	Max Dev
Lump 1	3.6	4.0	3.8	3.6	3.9	4.1	0.5	3.80	6.3%
Lump 2	3.5	3.5	3.2	3.4	3.3	3.3	0.3	3.36	4.8%
Lump 3	2.1	2.2	2.3	2.4	2.5	2.6	0.5	2.35	11.6%
Lump 4	1.5	1.8	1.5	1.9	1.6	1.6	0.4	1.65	9.1%
Lump 5	1.4	1.5	1.4	1.5	1.4	1.5	0.1	1.47	4.8%
Lump 6	1.0	1.1	0.9	1.1	0.7	0.8	1.1	0.93	24.8%

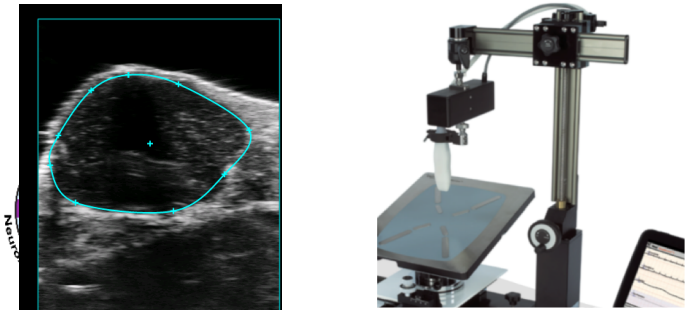
Processing face samples



Available measurement tools for cNF

Digital calipers

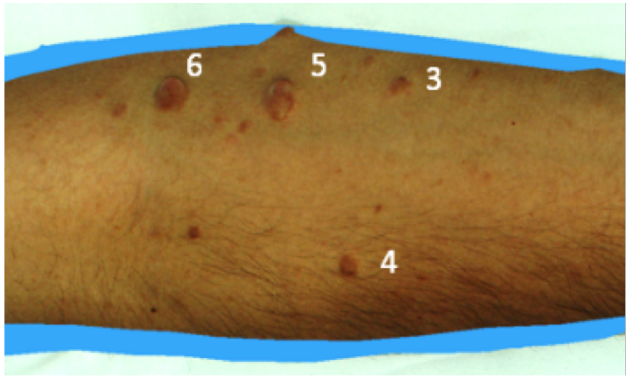
3D photography



HFUS

Increasing Complexity/cost

Calipers:
Conceptually simple
Inexpensive
Challenging for small tumors
Cannot visualize beneath skin
Reproducibility of caliper measurements on plastic model tumors is > 0.99



3D Photography:
Well established technology
Moderately expensive
Cannot visualize beneath skin
Captures other features of cNF

cNF are easily visualized on high frequency ultrasound (HFUS)

- 29 patients, 108 Neurofibromas
- Study aim: describe the sonographic appearance of different types of neurofibromas in patients with NF1 using High Frequency Ultrasound (HFUS)
- Easily visualized as hypoechoic masses in the dermis or hypodermis

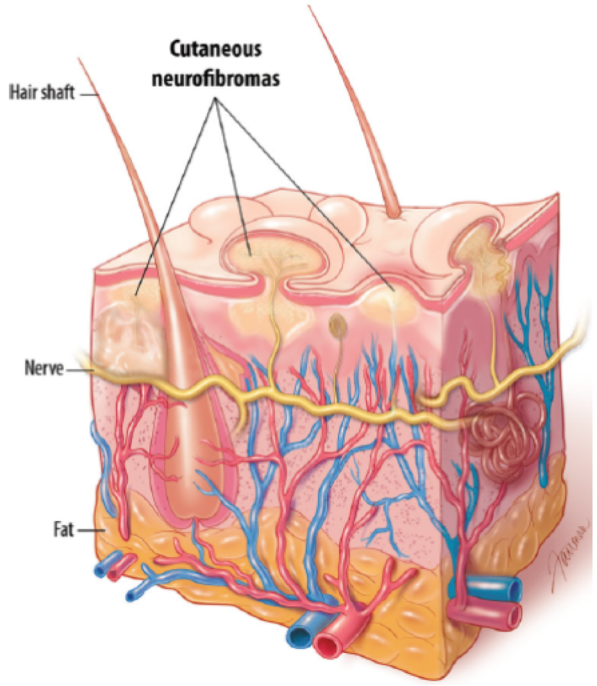
Table 1. Sonographic features of 108 neurofibromas using 25-MHz high-frequency ultrasound (HFU). Isoechogenicity was defined as normal dermal echogenicity.

Location	*n* (%)
Dermis	81/108 (76%)
Hypodermis	23/108 (21%)
Dermis and hypodermis	4/108 (3%)
Surface	
Fairly flat	81/108 (75%)
Protruding	27/108 (25%)
Contour	
Well-defined	60/108 (48%)
Poorly-defined	48/108 (44%)
Global echogenicity	
Hypoechoic	108/108 (100%)
Hyperechoic	0 (0%)
Echogenicity	
Homogeneous	67/108 (62%)
Heterogeneous	41 (38%)
Posterior acoustic feature*	
Enhancement	31/101 (31%)
Shadowing	0
Shape	
Smooth	65/108 (60%)
Spiked	25/108 (23%)
Rounded	17/108 (16%)
Spiked and rounded	1/108 (1%)
Pattern	
Plexiform	8/108 (7%)

*A posterior accoustic feature was not investigated in seven lesions exceeding the maximum depth (7 mm) using the 25-MHz probe.

Raffin et al, Eur J Dermatol, 2017

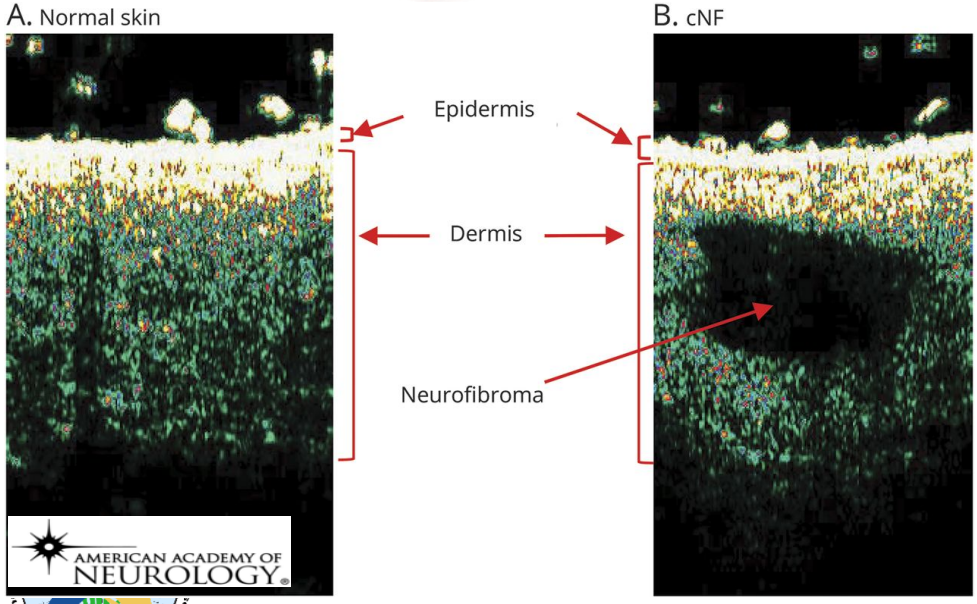
Anatomy of the skin



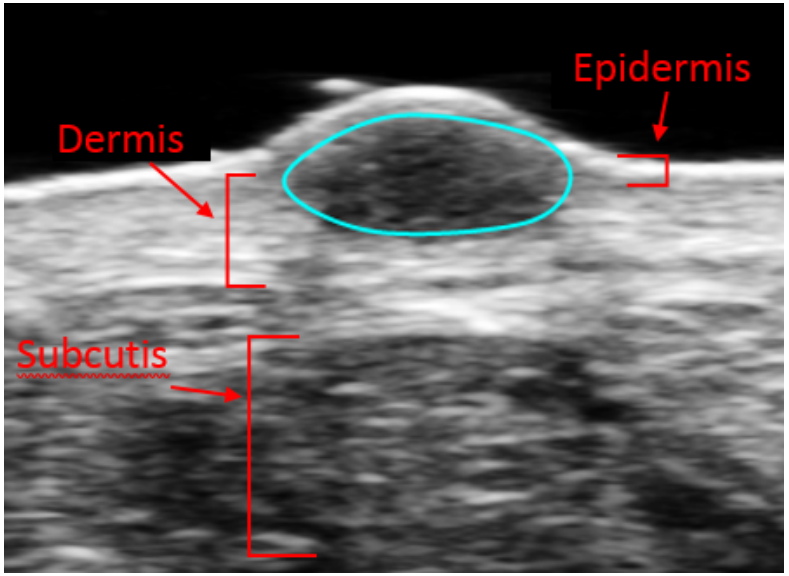
] Epidermis (barrier layer)

Dermis (contains connective tissue, hair follicles, and various cells)

Hypodermis (=subcutis, contains fat and connective tissue)



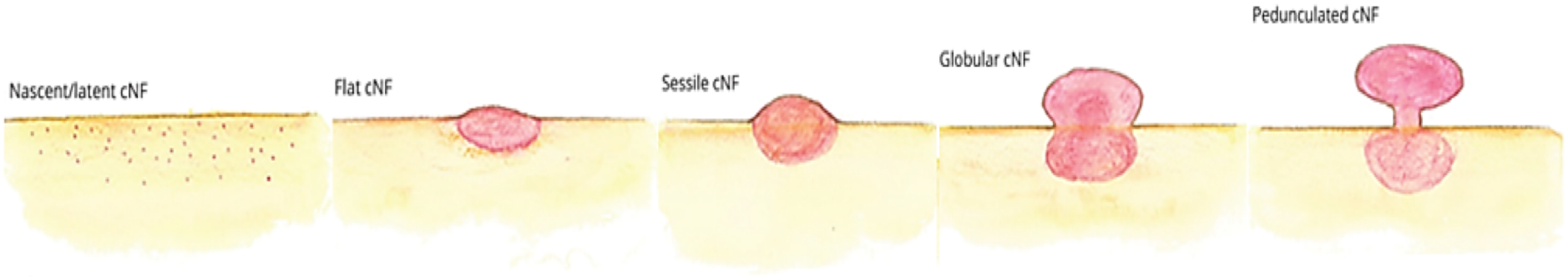
20-MHz transducer

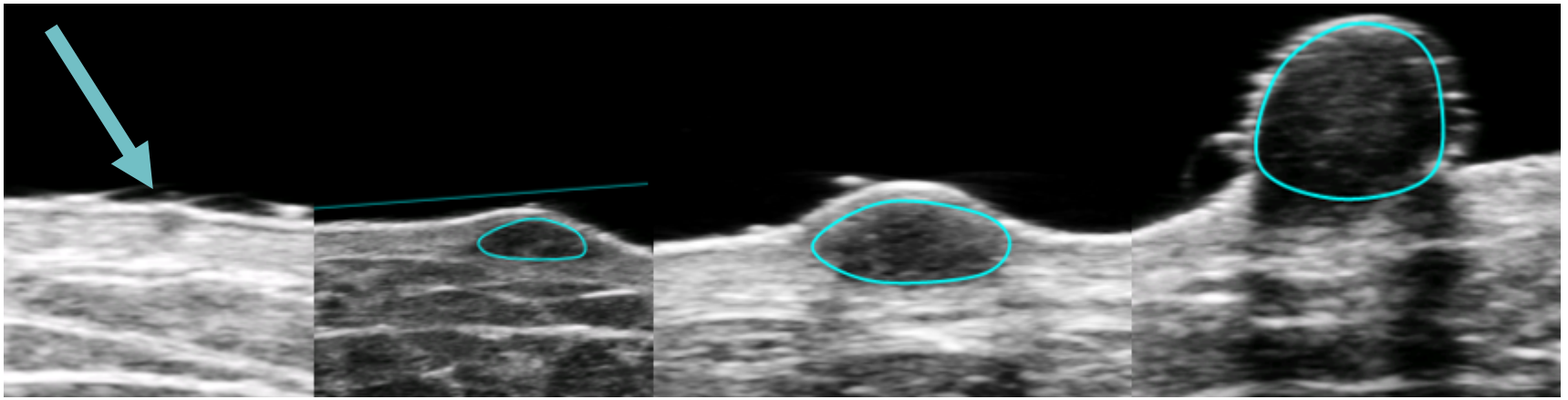


30-MHz transducer

Ashley Cannon et al.
Neurology 2018;91:S31-S37

Using HFUS to image cNF of Various Sizes





Project Aims

- Primary aim:
  - Determine the intra-rater and inter-rater reliability of HFUS measurements of cNF volume at baseline

- Secondary aim:
  - Determine the accuracy of HFUS measurements by comparing them to caliper measurement and digital photographs
  - Assess sensitivity to change over time HFUS

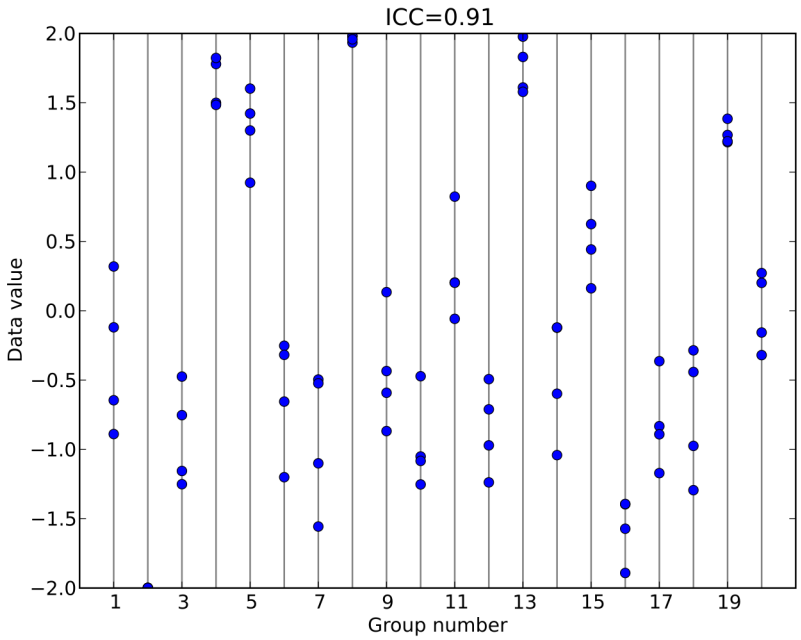
Methods

2 Study Components:

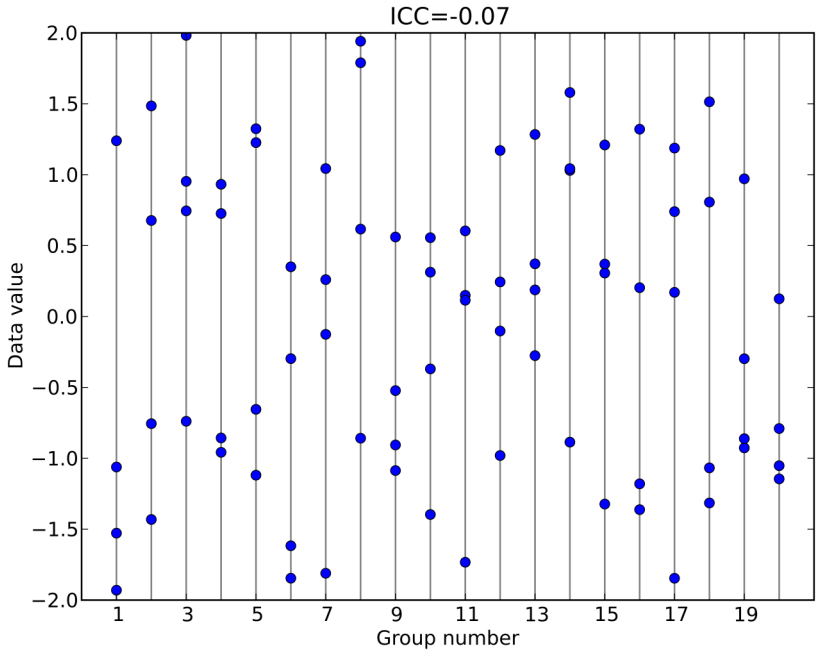
- Reproducibility evaluation using 27 tumors from first 5 patients to assess intra- and inter-rater reliability of digital calipers, 3D photography, and HFUS. Assessed reliability of:
    - *Image acquisition*: To test whether having different people acquire images affects reliability
    - *Image measurement*: To test weather having different people measure images affects reliability
- Longitudinal evaluation for all patients, to assess tumor growth over time (1 year)
    - Useful for clinical trial planning

Statistics

- Tumor assessments are compared using Intraclass Correlation Coefficient (ICC) to determine the intra- and inter-rater reliability of each measurement technique



Values from the same group tend to be similar



There is no tendency for values from the same group to be similar

Measurement types

- Linear measurements
  - Calipers, HFUS
  - Faster, easier
- Volumetric measurements
  - Calipers (calculated volume), 3D photography, HFUS
  - Less subject to positioning artifact

Reliability evaluation

- Assess variability in
  - image acquisition (e.g., taking of photograph)
  - Image measurement (e.g., measurement of photograph)
- Estimate variability attributed to
  - Inherent variability for each individual (intra-rater reliability)
  - Variability across individuals (inter-rater reliability)

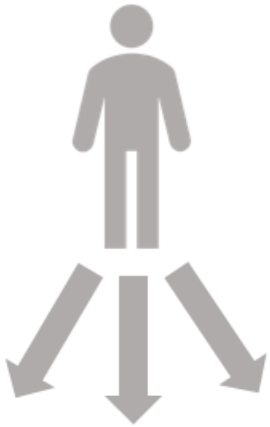
Demographics of participants

Feature	Value
Number (n)	5
Age (mean, years)	48.6 (range 36-65)
Sex (female)	3 (60%)
Ethnicity Non-Hispanic Hispanic	 4 (80%) 1 (20%)
Race White Asian	 4 (80%) 1 (20%)
Cutaneous neurofibromas (n)	27
Mean diameter (range) – mm < 5 mm ≥ 5 mm	5.1 (2.68-13.57) 16 (59%) 11 (41%)

Intra-rater ICC Results

	Image Acquisition ICC	Image Measurement ICC
Calipers		
Width	N/A	0.94
Length	N/A	0.90
Height	N/A	0.83
Volume	N/A	0.94
3D Camera		
Volume	0.96	0.94
HFUS		
Width	0.96	0.92
Height	0.97	0.95
Volume	0.98	0.98

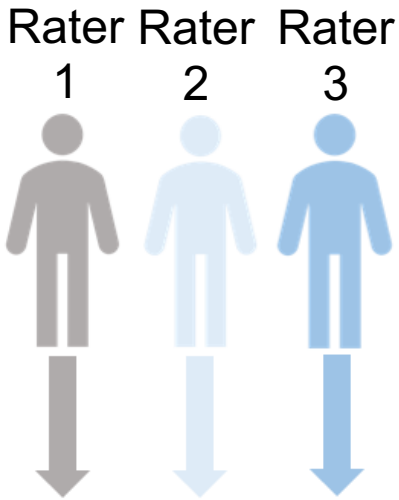
Rater 1



ICC	Reliability
<.05	Poor
0.5-.75	Moderate
0.75-0.9	Good
0.9-1.0	Excellent

Inter-rater ICC Results

	Image Acquisition ICC	Image Measurement ICC
Calipers		
Width	N/A	0.78
Length	N/A	0.71
Height	N/A	0.59
Volume	N/A	0.78
3D Camera		
Volume	0.95	0.97
HFUS		
Width	0.92	0.92
Height	0.96	0.97
Volume	0.95	0.91



ICC	Reliability
<.05	Poor
0.5-.75	Moderate
0.75-0.9	Good
0.9-1.0	Excellent

Discussion

- **Results are limited (so far) to cNF 14 mm or less in size**
- Image acquisition
  - Excellent reproducibility for photography and HFUS
  - (No data on calipers)
  - Minimal training is necessary for operators of photography and HFUS

- Image analysis
  - Photography and HFUS: Excellent reproducibility, regardless of analyst
  - Calipers: Reproducibility is better for single analyst (same person) than for multiple analysts (different people) → same person should be measuring these tumors. Also, measuring height introduces most variability

Discussion

- Each technique has strengths/weaknesses
  - Caliper: inexpensive, ICC in “good” range but worst for measurement of height. Primary variation is between measurers; cannot image below skin
  - Photography: moderately expensive, ICC is excellent for image acquisition and measurement; cannot image below skin; may be difficult with hair
  - HFUS: expensive, ICC is excellent for image acquisition and measurement, can image below the skin; can image early lesion in dermis
- Next steps: measuring sensitivity to change to determine thresholds for progression and response

Understanding prior approvals from FDA

Disease	Pathophysiology	IGA features
Psoriasis	Inflammation	Thickening and coloration
Eczema	Inflammation	Erythema, induration, lichenification
Rhytides	Structural	Depth and length
epidermal cGVHD	Inflammation	Erythema, scale, papules
Infantile hemangioma	Tumor	Resolution of hemangioma
Basal cell carcinoma	Tumor	Reduction of lesion size, ulceration

Proposition: primary endpoint must reflect pathophysiology of disease!

- Inflammatory conditions → look for clearance of inflammation
- Tumors with documented CR to meds (IH) → look for near/complete resolution
- Tumor without documented CR to meds (BCC) → look for reduction in size

→ for cNF, we can expect shrinkage (like BCC) but not resolution (like IH)

Clinical trial design for cNF

- Early vs. late phase development: **Is the drug active? vs. Does it provide clinical benefit?**
- Treatment vs. prevention design
- Systemic vs. local delivery

Proposed trial design for treatment trial of *raised cNF* to identify active drugs

- Region of interest: Patient selects 10 x 10 cm area of skin as target area to ensure changes are relevant
- 3D photograph of region of interest
  - Allows for assessment of multiple tumors and for central review
  - in future, consider whole body 3D photograph for systemic drugs
- Assessable lesions within ROI: at least XX mm in size, able to be photographed
  - Non-assessable lesions – too small, obscured by hair, etc.
- Primary endpoint: change in total volume of assessable lesions within region of interest
- Response criteria for primary endpoint: imaging response
  - Xx% reduction in total lesion volume of assessable lesions from baseline by photographic assessment
  - Xx% to be decided based on validity studies (sensitivity to change)

Key secondary endpoints: patient benefit

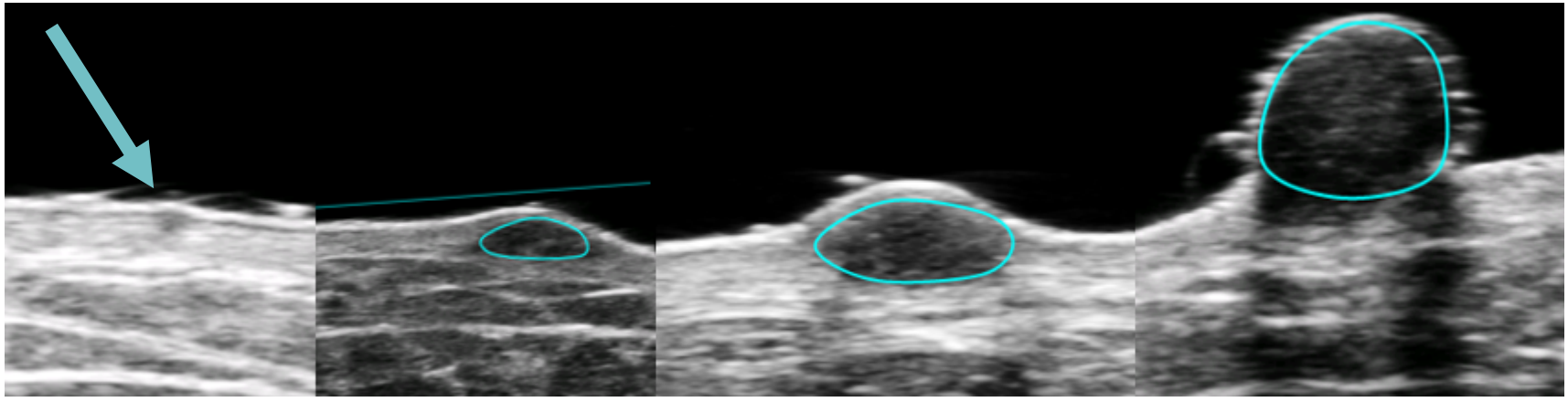
- Investigator global assessment (IGA)
  - Under development by cNF working group
  - Major response: Increase in IGA of 2 (4→2, 3→1)
  - Minor response: Increase in IGA of 1 (4→3, 3→2)
- PRO: Skindex, DLQI, or others
  - Need response criteria for PROs
  - To refine during early phase cNF studies in preparation for late phase studies
- Biomarkers:
  - Ultimate vision is to have biomarker driven clinical trials
  - to be discussed by Dr. Sarin

Proposed IGA

Score	Short descriptor	Detailed descriptor for region of interest (ROI)
0	Clear	No residual tumor; Scar or pigmentary change may be present
1	Almost clear	Flat tumors, may have discoloration
2	Mild	Low number and/or size of raised tumors that cause mild disfigurement of the underlying skin
3	Moderate	Moderate number and/or size of raised tumors that cause moderate disfigurement of underlying skin
4	Severe	High number and/or size of raised tumors that cause severe disfigurement of underlying skin

Design of prevention trials of cNF

- Drugs that can prevent growth of cNF would represent significant benefit for patients
- For small tumors, could use HFUS but need method to identify region of interest for imaging
- Need primary endpoint – size or number?
- Best secondary endpoints?
- Essential to have control – either historical control or placebo control
- Trial duration would likely be extended (although highly sensitive imaging can shorten duration)



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