Imaging Techniques for Neurofibromatosis Type 1-Associated Cutaneous Neurofibromas: Existing Approaches and Advancements

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Background

Neurofibromatosis type 1 (NF1) is a tumor predisposition syndrome caused by pathogenic variants in the NF1 gene. Cutaneous neurofibromas (cNFs), the predominant manifestation of NF1, can number in the thousands, resulting in substantial discomfort and disfigurement. A major limitation in advancing therapies is a lack of validated approaches for evaluating cNFs. Standardized measurement techniques must be applied to reliably assess the efficacy of treatments for these tumors.

Objective

This review presents the available data on existing and emerging techniques for identifying, measuring, and tracking cNFs.

Methods

A comprehensive search across Pubmed, Google Scholar, and clinicaltrials.gov was performed. Sources were assessed for the purpose of imaging and readouts addressing reliability, reproducibility, feasibility, and capabilities when assessing cNFs.

Results

Seven manuscripts published from 2008-2022 and eight clinical studies focused on cNF imaging techniques were identified. These measurement techniques included calipers, digital imaging, high-frequency ultrasound sonography (HFUS), spatial frequency domain imaging (SFDI), and optical coherence tomography (OCT).

Calipers prove useful for cNFs measuring at least 5 mm; however, time required for measurement of each cNF, measurement variability, and lack of raw data storage are limiting factors. 2D digital imaging is accessible to clinics and patients as phone cameras can be utilized, allowing crowdsourcing of data and potential supplementation of medical grade images for cNF assessment. 3D image capture, including whole-body imaging, facilitates longitudinal tracking of cNFs. HFUS demonstrates high measurement reliability and allows visualization of cNF features below the skin surface. New techniques applied to other dermatologic conditions such as SFDI and OCT are being repurposed for cNFs to enable earlier detection of cNFs and augment trials focused on preventative treatment. The cost of each technique, user training, and median time for image or measurement acquisition and analysis varied significantly (Figure 1).

Conclusion

Accurate and efficient detection, tracking, and evaluation of change for cNFs are critical to address the unmet medical need of these tumors. Calipers, 2D/3D imaging, and HFUS have shown utility in this context. SFDI and OCT can potentially detect nascent cNFs. However, the need to assess tumors involving dermis beneath and above the skin surface and the variable phenotype of cNFs (in size, morphology, color, location, growth rate, abutment with other tumors) make imaging challenging. With a growing array of cNF therapeutic options in development, further work is needed to pinpoint optimal imaging technique applications aligned with specific cNF study goals.

Imaging modality used	Estimated Cost of Hardware and Software ($)	Capabilities/Advantages	Disadvantages
Digital Calipers	$50-$500	❖ Measure length, width, height of individual cNF ❖ Recommended for measuring longest diameter of large (5mm or greater) cNFs	❖ Cannot measure depth below skin surface, does not assess cNF morphology ❖ Low reliability when measuring cNF height ❖ Not recommended for measuring small cNFs (<5 mm) ❖ Time consuming when measuring numerous cNFs ❖ Does not generate a permanent record
3D Photography - Vectra H1 3D camera	$11,800 -$13,400	❖ Measure volume, surface area, width, and length of cNF for large skin areas ❖ Portable handheld camera ❖ Little training required to operate	❖ Requires training for software use and unable to measure cNF height ❖ cNF parameters must be measured separately ❖ Variability in counting cNFs that are superimposed ❖ 3D model image quality is disturbed by bodily hair
3D Photography - LifeViz Micro	$19,500	❖ Portable handheld camera and little training required to operate ❖ cNF parameters (length, width, height, volume) measured and provided simultaneously	❖ Variability in counting cNFs that are superimposed ❖ 3D model image quality is disturbed by bodily hair
3D Photography - Cherry Imaging	$23,600	❖ Portable handheld camera ❖ cNF parameters (length, width, height, volume) measured and provided simultaneously	❖ Contraindicated for use on patients with epilepsy ❖ Training required to operate effectively ❖ Scanner can only be used whilst connected to a laptop, limiting portability ❖ 3D model image quality is disturbed by bodily hair
Whole Body 3D Photography - Canfield Vectra WB360	$250,000	❖ Image of all exposed skin surfaces ❖ Tagging and annotation of large number of cNFs is feasible	❖ Cannot measure depth of tumor below skin surface ❖ Lack of portability; requires a dedicated room and trained operator ❖ Costly equipment and maintenance
High Frequency Ultrasound Sonography	$225,000	❖ Measure volume, width, and depth (above and below skin) ❖ Assess skin layer position, surface characteristics, margins, echogenicity, posterior acoustic enhancement, linear lateral extension, and plexiform pattern of cNFs	❖ Requires training in ultrasound technique, image optimization, and software ❖ Difficult to find and track large number of cNFs
Spatial Frequency Domain Imaging	$63,000	❖ Quantify tissue optical properties over large surface areas (10 x 20 cm), allowing detection of nascent cNFs ❖ Portable device smaller than cart-based ultrasound	❖ Extensive training required for image acquisition and analysis ❖ Technology is relatively new and validation research is still ongoing
Optical Coherence Tomography	$87,000	❖ Permit cross-sectional view of lesion *in vivo* and visualization of vascular properties and microstructure, dermal-epidermal junction, and dermal layers	❖ Extensive training required for image acquisition and analysis

Figure 1: Imaging and measurement modalities for NF1-associated cutaneous neurofibromas

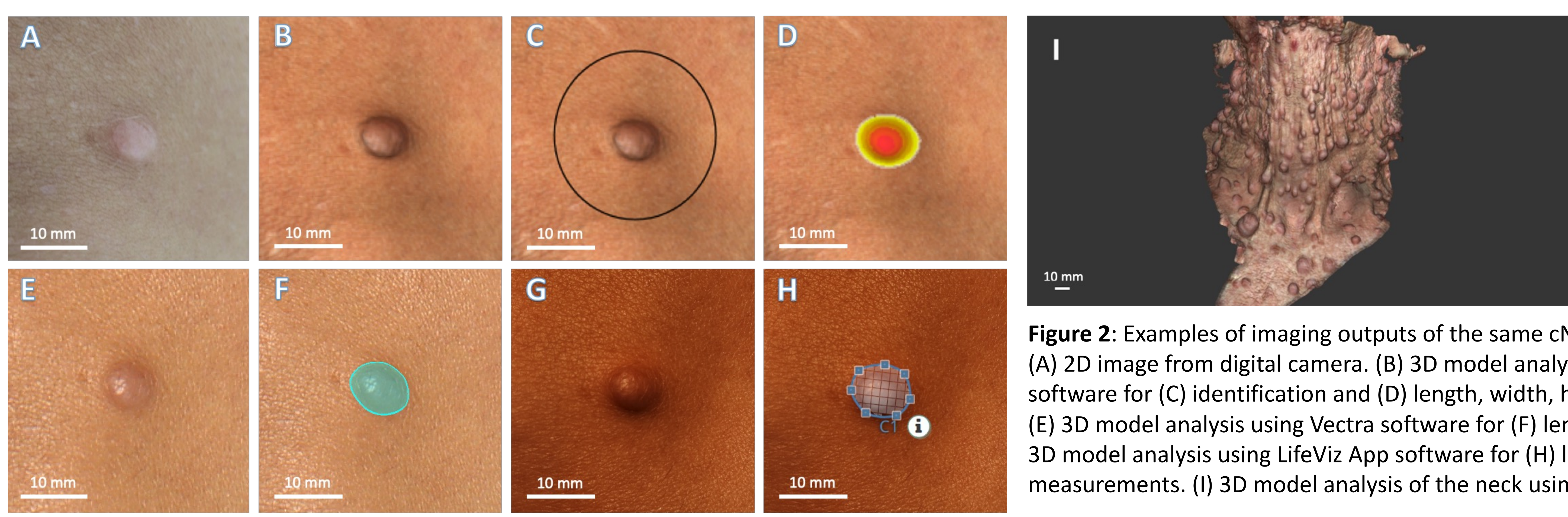

Figure 2: Examples of imaging outputs of the same cNF using different camera systems (A) 2D image from digital camera. (B) 3D model analysis using Cherry Imaging Trace software for (C) identification and (D) length, width, height, and volume measurements. (E) 3D model analysis using Vectra software for (F) length and width measurements. (G) 3D model analysis using LifeViz App software for (H) length, width, height, and volume measurements. (I) 3D model analysis of the neck using Cherry Imaging Trace software.

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