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Recognizing the benefits and pitfalls of reflectance confocal microscopy in melanoma diagnosis

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The incidence of melanoma has been on the rise for the last several decades, with a current US lifetime risk of developing melanoma estimated as 1 in every 60 individuals [1]. The key to preventing death from melanoma is the early detection of this cancer, at a stage where surgical excision is curative. However, in attempt to diagnose melanoma early, physicians are also removing many benign lesions, most of these being melanocytic nevi.

The pursuit to improve our clinical sensitivity for melanoma diagnosis, while minimizing unnecessary skin biopsies, has led to the development of skin imaging techniques. Among recent non-invasive imaging modalities, reflectance confocal microscopy (RCM) stands out as particularly promising since it offers bedside imaging at cellular-level resolution. Stevenson and coauthors [2] have reported in *Dermatology Practical & Conceptual* on a systematic review of the diagnostic accuracy of RCM for melanoma diagnosis. They have identified five publications, including a total of about 900 lesions, a third of which were melanomas; most of these lesions were reportedly equivocal for diagnosis, clinically and dermatoscopically. Based on these studies, the pooled sensitivity for melanoma diagnosis using RCM is 93% (range 91%-97%) and specificity is 76% (range 68%-86%). While the study by Stevenson et al [2] did not address the exact contribution of RCM as an add-on test to dermatoscopy, the aforementioned data suggests that RCM can indeed increase diagnostic accuracy beyond clinical and dermatoscopic examination.

To simulate the added contribution of RCM to dermatoscopy, Stevenson et al [2] took a hypothetical case of 1000 dermatoscopically equivocal skin lesions, and based on the previously reported benign to malignant ratio of 4:1 for experts' diagnosis of melanoma [3], they assume a ratio of 800 benign lesions to 200 melanomas. They estimate that RCM will prevent the unnecessary excision of 608 benign lesions that would be diagnosed as benign based on RCM, reflecting the specificity of 76%. If we were to formulate the best indications for using RCM as an add-on test to dermatoscopy, we would need to better point-out which lesions are included in this group of 608 benign lesions that are dermatoscopically equivocal, but RCM negative. In this editorial, we can only attest to our own impression and experience, as well as some literature reports, that this group of lesions could encompass the following examples:

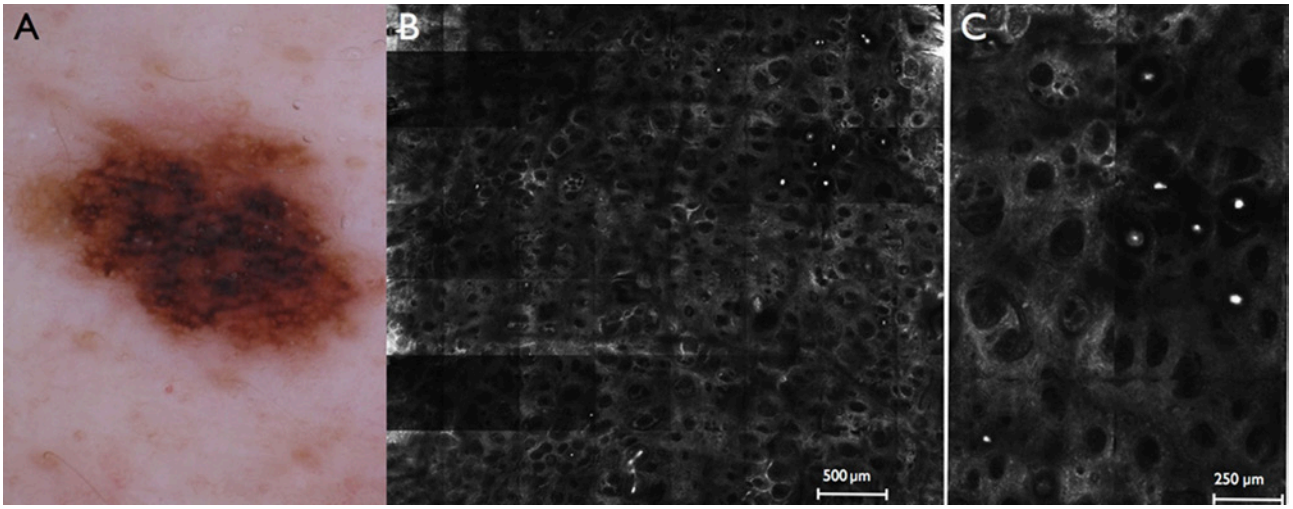

Figure 1. (A) Dermatoscopic image of a nevus showing an irregular network with thickened dark brown lines. (B) RCM mosaic (3.5 x 3.5 mm) acquired at dermo-epidermal junction level reveals a regular Ringed and Meshwork pattern. (C) Higher magnification RCM image (1.5 x 1 mm) depicts well-outlined dermal papillae in the absence of atypical cells, features compatible with the diagnosis of a nevus. [Copyright: ©2014 Scope et al.]

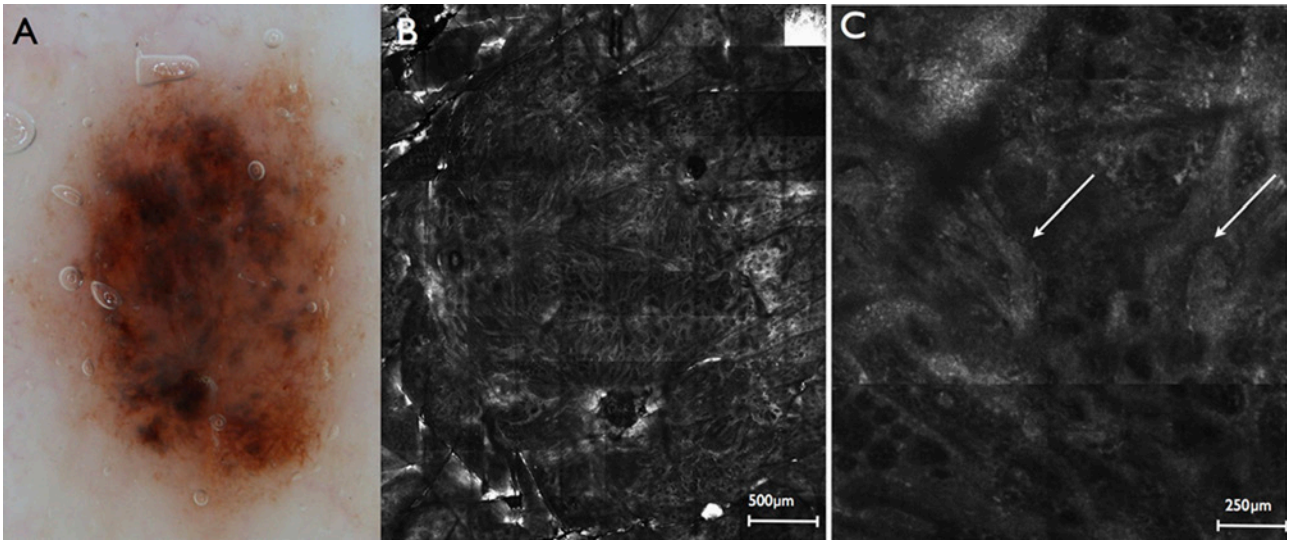

Figure 2. (A) Dermatoscopy image of a nevus typified by complex pattern with central bluish clods, structureless areas and peripheral network. (B) RCM overview image (5 x 6 mm mosaic) acquired at dermo-epidermal junction level reveals a regular Meshwork pattern. (C) Higher magnification RCM image (1.5 x 1 mm) shows junctional thickening and junctional nests in the absence of atypical cells, features compatible with the diagnosis of a nevus. [Copyright: ©2014 Scope et al.]

(1) nevi with irregular pigment pattern (e.g., irregular network, complex pattern) on dermatoscopy showing a regular pattern (e.g., ringed or meshwork patterns) on RCM (Figures 1,2);
(2) nevi with a hyperpigmented structureless pattern on dermatoscopy that display on RCM a cobblestone pattern of the epidermis (reflecting pigmented keratinocytes at the basal and suprabasal epidermis) or a dense infiltrate of melanophages in the dermis;
(3) a dermatoscopically-equivocal lesion on sun-damaged skin with a differential diagnosis between solar lentigo and melanoma on sun-damaged skin, that presents a straightforward pattern of solar lentigo on RCM, without any findings concerning for melanoma;
(4) a pink macule revealing only a vascular pattern on dermatoscopy, while RCM demonstrates a straightforward pattern of nevus;
(5) a macule or patch displaying granularity or blue-gray hue on dermatoscopy, while showing on RCM features of lichen planus-like keratosis with melanophages and remnants of solar lentigo, in the absence of suspicious findings for melanoma [4];
(6) recurrent pigmentation in a scar, whereby RCM helps discriminate between a benign reactive pigmentation and an atypical melanocytic proliferation which would require a biopsy to exclude melanoma [5].

However, there is also a "price" associated with overriding dermatoscopic concern with RCM-based diagnosis. In the

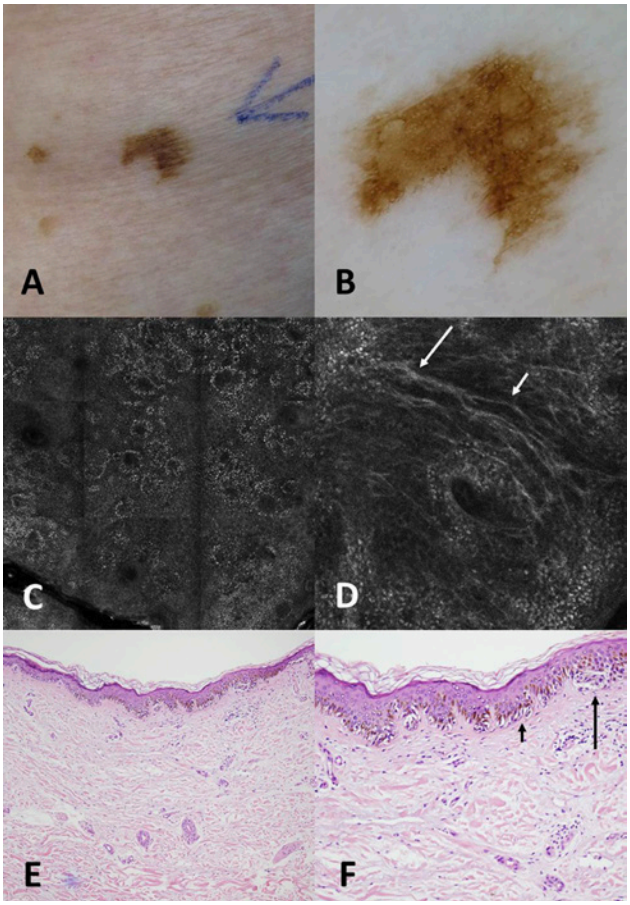

Figure 3. (A) Clinical image of a 10 mm asymmetric brown patch on the right leg. The patient is a 64-year-old female with prior history of melanoma, and the lesion has been present for several years without notable change. (B) Dermatoscopic image showing an irregular reticular pattern. The differential diagnosis was between solar lentigo and melanoma on sun-damaged skin. (C) RCM mosaic image (1.5 x 1.5 mm) acquired at dermo-epidermal junction level reveals a Ringed pattern. The initial RCM diagnosis was that of a nevus. However, more exhaustive imaging (akin to "step sectioning" on histopathology) was done as clinically and dermatoscopically, the lesion did not fit well with a nevus. (D) RCM image (0.5 x 0.5 mm) at the level of the basal layer of the epidermis showed foci with irregular infiltration of bright dendritic cells as solitary units (arrowhead) and as aggregates (arrow). The final RCM diagnosis was melanoma. (E) On histopathology (hematoxylin & eosin, 10x), there is a broad asymmetric junctional proliferation of melanocytes, compatible with a melanoma in situ. (F) Higher magnification histopathology (hematoxylin & eosin, 20x) shows the tissue correlates of the RCM findings; atypical dendritic melanocytes are seen as crowded solitary units (arrowhead) and as aggregates (arrow). [Copyright: ©2014 Scope et al.]

estimation by Stevenson et al [2] among the 200 melanomas that are deemed for excision based on the dermatoscopic impression, 14 melanomas may be misdiagnosed as benign based on the RCM findings, reflecting an imperfect sensitivity of 93%. If we were to improve in recognizing the pitfalls of RCM, we would need to identify recurring patterns among these 14 melanomas. Again, based on personal experience and literature reports, here are some potential examples of RCM-false negative melanomas: (1) nodular melanoma associated with hyperkeratosis or ulceration [6]; (2) fully ulcerated melanoma, a scenario where RCM should not be used, since secondary surface changes (e.g., blood, scale-crust) can obscure diagnostic findings; (3) nevoid type melanoma consisting cytologically of mostly of small-melanocytes [7]; and (4) melanoma in situ showing on RCM only focally suspicious findings for melanoma, while displaying equivocal reticular pattern on dermatoscopy (Figure 3). We also need to develop strategies to minimize the rate of RCM false-negative melanomas. As a general rule, good agreement between clinical, dermatoscopic and RCM findings should be reached to minimize the risk of missing melanomas. We need to remember that RCM is an adjunct test that should be integrated with other diagnostic data. In this regard, there is a difference between flat and nodular equivocal lesions. Flat lesions with significant clinical and dermatoscopic suspicion that are diagnosed as benign based on RCM imaging, should still be strongly considered for digital dermatoscopic monitoring. In contrast, for nodular lesions a dichotomous decision, biopsy or not, should always be obtained; nodular lesions that do not show clear-cut benign findings on RCM in a way that correlates well and accounts for the dermatoscopically-concerning findings, should be strongly considered for biopsy.

Finally, in the simulated scenario discussed by Stevenson et al [2], sensitivity for diagnosis was assumed to be set by dermatoscopy, as RCM examination is only performed on dermatoscopically-equivocal lesions that are otherwise deemed for excision. Indeed, a common point of view is that RCM cannot impact sensitivity for melanoma diagnosis beyond clinical and dermatoscopic examination. However, management decisions in the clinic are more complex and influenced by the physician's (A) interpretation of the lesion's morphology, (B) diagnostic confidence and (C) threshold for biopsy, to name a few factors. In real life, not all lesions referred for RCM imaging would have evoked a biopsy based on clinical and dermatoscopic findings alone (Figure 4). As RCM becomes more readily available at the bedside, in terms of cost, size of device, ease and speed of use, the clinical and dermatoscopic thresholds for referring lesions to RCM examination may be much lower than the thresholds, which prompt a biopsy. For example, in individuals with very fair skin where many skin lesions appear pink or non-pigmented, RCM can add diagnostic information and narrow the broad differential diagnosis between BCC, Bowen's disease, nevus, amelanotic melanoma and inflammatory lesions [8]; in this scenario, the handheld RCM device, which allows for more rapid screening of multiple lesions, can be particularly useful for guiding the clinician which of the pink lesions needs to be biopsied [9]. Another example is a small-diameter pigmented lesion with few and equivocal dermatoscopic findings, while

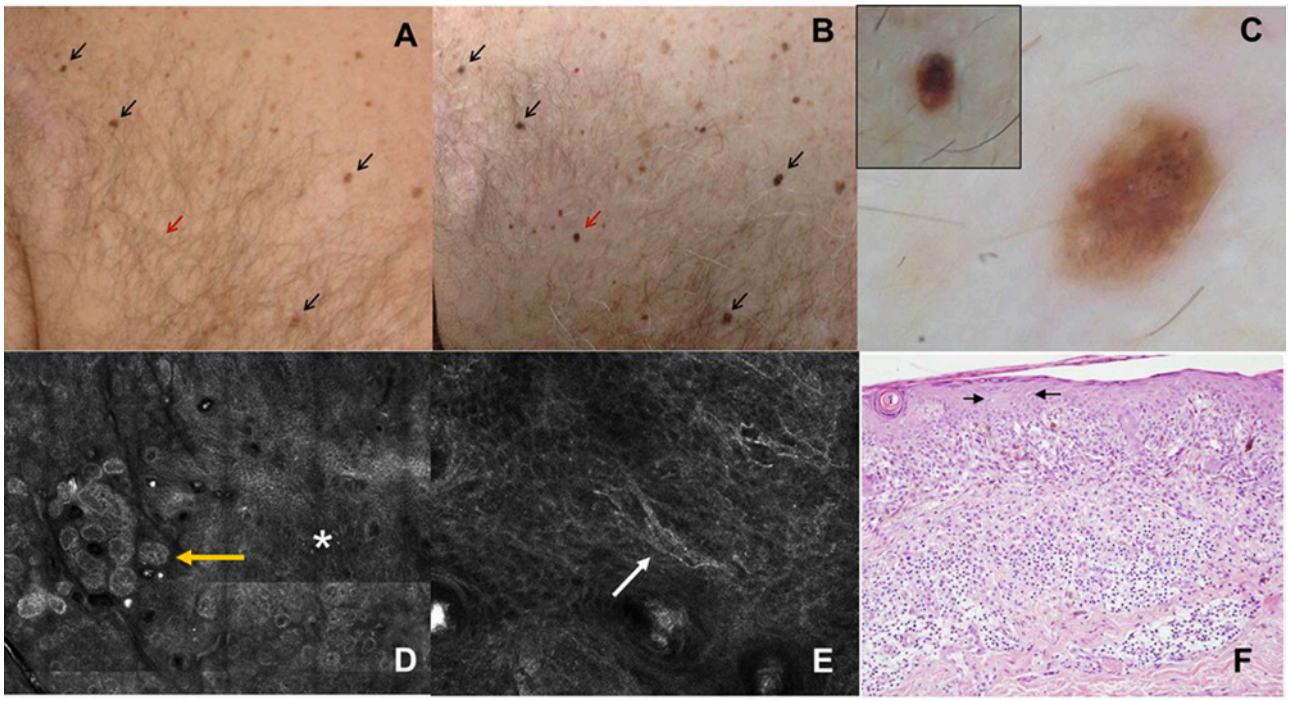

Figure 4. (A) Baseline back images of a 69-year-old male patient with a history of melanoma. (B) Repeat back image, at 3-year follow-up, reveals a new pigmented macule on the left upper back (red arrow). Of note, the arrows in (A) and (B) correspond to the same anatomic locations. (C) Clinically (inset) the lesion is a symmetric 5 mm macule with 2 shades of brown. Dermatoscopically, the lesion displays a homogenous pattern, with brown-gray dots. The suspicion for melanoma was very low at this juncture, but the patient was referred to RCM because the lesion was new. (D) RCM mosaic (2.5 x 2 mm) acquired at the level of the basal layer of the epidermis shows an irregular Ringed (yellow arrow) and non-specific pattern (white asterisk). (E) On higher magnification RCM image (0.5 x 0.5 mm) at the spinous layer of the epidermis, dendritic cells in pagetoid pattern can be seen. The RCM diagnosis is melanoma. (F) On histopathlogy (hematoxylin and eosin, 20X), there are irregularly crowded nests of atypical melanocytes at the DEJ, lack of dermal maturation, and atypical melanocytes in pagetoid pattern (arrows). The diagnosis is melanoma 0.6 mm in Breslow thickness. [Copyright: ©2014 Scope et al.]

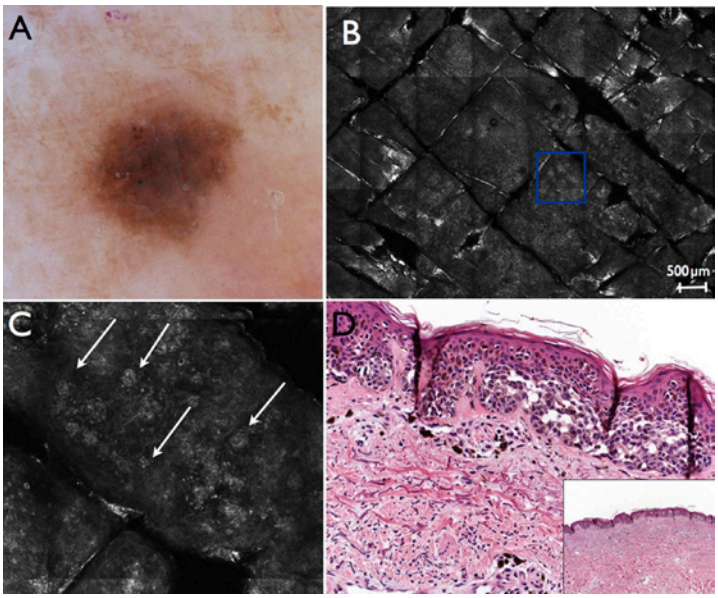

Figure 5. (A) Dermatoscopy image of a 3 mm pigmented lesion. Dermatoscopy reveals a structureless brown-gray pigmentation with few dots. (B) RCM mosaic (3.5 x 2.5 mm) acquired at the level of the spinous-granular layers of the epidermis displays a disarrayed pattern of the epidermis with bright cells in pagetoid distribution at the periphery of the lesion (blue square). (C) On higher magnification RCM image (1.25 x 0.75 mm), large and bright nucleated cells in pagetoid pattern (arrows) can be easily detected. The RCM diagnosis for this lesion is melanoma. (D) On histopathology (hematoxylin and eosin, 20X), there is a junctional proliferation of atypical melanocytes as confluents nests and as solitary units, as well as melanocytes in pagetoid pattern. The diagnosis is melanoma 0.3 mm in Breslow thickness. [Copyright: ©2014 Scope et al.]

RCM shows features that are highly suspicious for melanoma (Figure 5) [10].

In conclusion, RCM is rapidly becoming an important add-on tool in the armamentarium of dermatologists who screen patients for skin cancer. Incorporating RCM as a diagnostic adjunct can increase specificity of melanoma diagnosis. However, we need to study more extensively the indications for using RCM, and equally importantly, the limitations of RCM.

References

1. Rigel DS. Epidemiology of melanoma. Semin Cutan Med Surg. 2010;29:204-9.
2. Stevenson AD, Mickan S, Mallett S, et al. Systematic review of diagnostic accuracy of reflectance confocal microscopy for melanoma diagnosis in patients with clinically equivocal skin lesions. Dermatol Pract Concept. 2013;3:19–27.
3. Carli P, De Giorgi V, Crocetti E, et al. Improvement of malignant/benign ratio in excised melanocytic lesions in the 'dermoscopy era': a retrospective study 1997-2001. Br J Dermatol. 2004;150:687-92.
4. Bassoli S, Rabinovitz HS, Pellacani G, et al. Reflectance confocal microscopy criteria of lichen planus-like keratosis. J Eur Acad Dermatol Venereol. 2012;26:578-90
5. Longo C, Moscarella E, Pepe P, et al. Confocal microscopy of recurrent naevi and recurrent melanomas: a retrospective morphological study. Br J Dermatol. 2011;165:61-8.
6. Longo C, Farnetani F, Ciardo S, et al. Is confocal microscopy a valuable tool in diagnosing nodular lesions? A study of 140 cases. Br J Dermatol. 2013;169:58-67
7. Guitera P, Menzies SW, Longo C, et al. In vivo confocal microscopy for diagnosis of melanoma and basal cell carcinoma using a two-step method: analysis of 710 consecutive clinically equivocal cases. J Invest Dermatol. 2012;132:2386-94.
8. Braga JC, Scope A, Klaz I, et al. The significance of reflectance confocal microscopy in the assessment of solitary pink skin lesions. J Am Acad Dermatol. 2009;61:230-41.
9. Fraga-Braghiroli NA, Stephens A, Grossman D, et al. Use of handheld reflectance confocal microscopy for in vivo diagnosis of solitary facial papules: a case series. J Eur Acad Dermatol Venereol. 2013 [Epub ahead of print]
10. Pupelli G, Longo C, Veneziano L, et al. Small-diameter melanocytic lesions: morphological analysis by means of in vivo confocal microscopy. Br J Dermatol. 2013;168:1027-33.