Reflectance confocal microscopy terminology glossary for nonmelanocytic skin lesions: A systematic review

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Background: There is lack of uniformity in reflectance confocal microscopy (RCM) terminology for nonmelanocytic lesions (NMLs).

Objective: To review published RCM terms for NMLs and identify likely synonymous terms.

Methods: We conducted a systematic review of original research articles published up to August 19, 2017, adhering to Preferred Reporting Items for Systemic Reviews and Meta-Analyses guidelines. Two investigators gathered all published RCM terms used to describe basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and seborrheic keratosis/solar lentigo/lichen planus–like keratosis (SK/SL/LPLK). Synonymous terms were grouped on the basis of similarity in definition and histopathologic correlates.

Results: The inclusion criteria was met by 31 studies. Average frequency of use per term was 1.6 (range 1-8). By grouping synonymous terms, the number of terms could be reduced from 58 to 18 for BCC, 58 to 36 for SCC, 23 to 12 for SK/SL/LPLK, and from 139 to 66 terms (52.5% reduction) in total. The frequency of term usage stratified by anatomic layer (suprabasal epidermis vs epidermal basal layer, dermoepidermal junction, and superficial dermis) was 27 (25.7%) versus 78 (74.2%) for BCC; 60 (64.5%) versus 33 (34.5%) for SCC, and 15 (45.4%) versus 18 (54.5%) for SK/SL/LPLK, respectively.

Limitations: Articles that were not peer reviewed were excluded.

Conclusion: Systematic review of published RCM terms provides the basis for future NMLs terminology consensus. (J Am Acad Dermatol 2019;80:1414-27.)

Key words: actinic keratosis; basal cell carcinoma; diagnosis; lichen planus-like keratosis; melanoma; nonmelanoma skin cancer; reflectance confocal microscopy; seborrheic keratosis; squamous cell carcinoma.

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Supplemental Figs 1-3 available at http://www.jaad.org.

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Reflectance confocal microscopy (RCM) enables noninvasive in vivo visualization of the skin at a quasihistologic resolution.[1] In the 1990s, the histologic correlates of RCM attributes of skin were first described.[2,3] Since then, >200 articles have been published showing the added value of RCM in the diagnosis of melanoma[4-6] and nonmelanoma skin cancer, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).[7-9] Also, RCM has been used for the diagnosis of nevi and benign nonmelanocytic skin lesions (NMLs).[10,11] Although the increase in number of RCM publications suggests a gradual wider adoption of this technique, there appears to be an inconsistent usage of RCM terminology in the literature. Furthermore, descriptive terms used for particular neoplasms, such as polarization of nuclei and epidermal shadow for BCC have shown to be associated with low interobserver agreement.[12]

CAPSULE SUMMARY

- Use of reflectance confocal microscopy terminology is inconsistent.
- We built a glossary of reflectance confocal microscopy terms for diagnosing nonmelanocytic lesions. We identified terms with similar definition and histopathologic correlates and reduced the total number of terms by 52.5%. This systematic review could be used to attain terminology consensus.

The first expert consensus on RCM terminology, published in 2007 by Scope et al, focused solely on melanocytic neoplasms.[13] To the best of our knowledge, consensus on terminology related to the diagnosis of malignant and benign NMLs is lacking. Recently, category I current procedural terminology reimbursement codes by the Centers for Medicare and Medicaid Services in the United States were allotted to RCM imaging.[1,14] As a result, increasing assimilation of RCM into routine clinical workflow and the dermatology residency curriculum is anticipated.[15] This forthcoming clinical integration necessitates standardization of RCM terminology so that structured reporting of RCM-based diagnosis is enabled and RCM teaching to novices can be facilitated. Herein, we performed a systematic review of terms used in original papers published during 1995-2017 to describe RCM features of common NMLs.

METHODS

The results of this systematic review were obtained according to the guidelines for reporting systematic reviews as published in the Preferred Reporting Items for Systemic Reviews and Meta-Analyses statement (www.prisma-statement.org). All images used were acquired at the Dermatology Service of Memorial Sloan Kettering Cancer Center, New York, New York, and Dermatology Associates, Plantation, Florida, using commercial RCM systems (Vivascope 1500 or Vivascope 3000, Caliber ID, Rochester, NY) and collected under an approved institutional review board retrospective protocol (no. 17-083). The basic principles of RCM image acquisition have been previously described.[1]

Eligibility criteria

We included all peer-reviewed original articles published by August 19, 2017, that contained the diagnosis of common benign and malignant NMLs, including BCC, SCC, actinic keratosis (AK), seborrheic keratosis (SK), solar lentigo (SL), and lichen planus–like keratosis (LPLK). We excluded NMLs that, in our experience, are relatively infrequently subjected to RCM imaging in current practice, such as poroma, clear cell acanthoma, dermatofibroma, atypical fibroxanthoma, and Merkel cell carcinoma, among others. We also excluded articles describing RCM features of NMLs at special anatomic sites, such as the genitalia, nails, and eyelids.

We excluded literature reviews, single case reports, conference abstracts, animal studies, and publications lacking full text. Due to the lack of the peer-review process, we also excluded book chapters.

Information sources, search, and study selection

Systematic literature searches were conducted (August 19, 2017) in 4 databases with no specified date, age, sex, or language restrictions. The databases searched were Medline (via PubMed), Embase, The Cochrane Library, and Web of Science. Search results were combined in the bibliographic management tool EndNote (Clarivate Analytics, Philadelphia, Pennsylvania), and duplicates were eliminated both electronically and manually to ensure an efficient deduplication process. The search strategy employed the medical subject headings phrases "microscopy, confocal" AND ("skin neoplasms" OR "dermatology" OR "carcinoma" OR "keratosis, actinic" AND "in vivo") AND ("terminology" OR "current procedural terminology" OR "terminology as topic" OR "dictionaries as topic" OR "data accuracy" OR "algorithms" OR

Abbreviations used:

AK: actinic keratosis
BCC: basal cell carcinoma
DEJ: dermoepidermal junction
LPLK: lichen planus–like keratosis
NML: nonmelanocytic skin lesion
RCM: reflectance confocal microscopy
SCC: squamous cell carcinoma
SK: seborrheic keratosis
SL: solar lentigo

"reproducibility of results" OR "classification"). Bibliographies within retrieved articles were also reviewed to identify additional studies. For this specific systematic review, we only included RCM terms pertinent to NMLs and excluded terms related to melanocytic neoplasms (ie, melanomas and nevi).

Two authors (Dr Navarrete-Dechent and Dr Jain) independently screened all relevant titles and abstracts for eligibility. If necessary, full-text articles were screened. Differences in judgment were resolved with a third reviewer (Dr Scope) until consensus was reached.

Data collection and extraction

Two authors (Dr Navarrete-Dechent and Dr Jain) extracted data from the included studies independently. Disagreements were resolved by consensus;

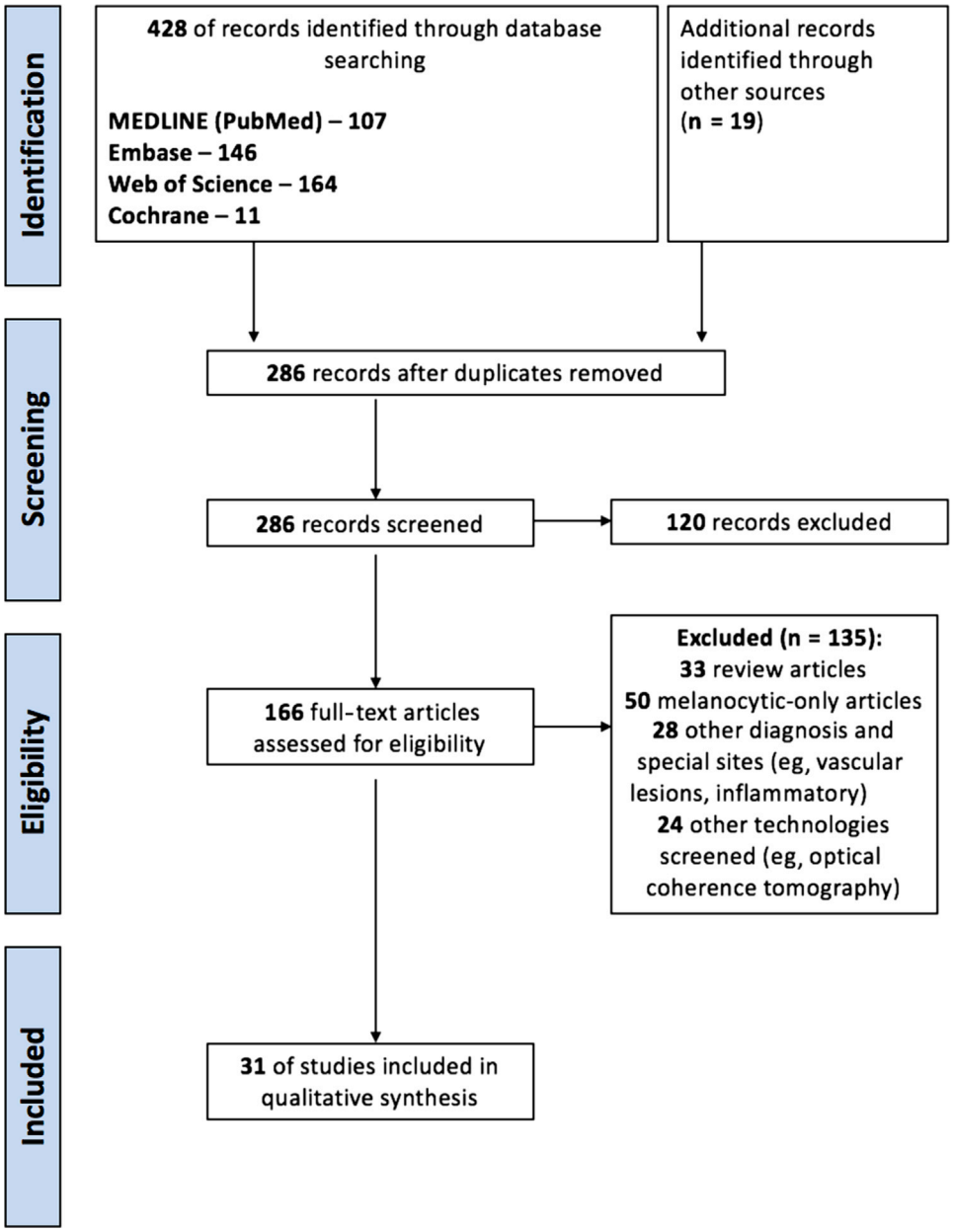

Fig 1. Preferred Reporting Items for Systemic Reviews and Meta-Analyses diagram.

Table I. Basal cell carcinoma RCM terms, frequency of use in the literature, and suggested grouping on the basis of similarity of definition and histopathologic correlates

RCM term	Use frequency of RCM term, n (%)	Definition	Histopathologic correlates
Suprabasal epidermis term (n = 13; 22.4%)			
Actinic changes in honeycomb[7,8,19]	3	Keratinocytic atypia with varying size of nuclei, pleomorphism, architectural disarray, parakeratotic nuclei	Keratinocytic atypia within the epidermis
Architectural disorder of overlying epidermis[18]	1		
Mild keratinocyte atypia[21]	1		
Atypical honeycomb pattern[6]	0‡		
Weighted subtotal*	**5 (4.7)**		
Elongated nuclei in the epidermis[7,8,19]	3	Elongated monomorphic basaloid nuclei both in the epidermis aligned in the same axis and underlying tumor nests	No known histopathologic correlate, probably the en face view of the uppermost part of a tumor nest or cord with palisading
Streaming of the epidermis[21-26]	6		
Polarization[19,27]	2		
Polarized in the honeycomb[6]	1		
Polarization of nuclei of the epidermis[7,8,19]	3		
Weighted subtotal*	**15 (14.2)**		
Prominent nucleoli[7]	1	Visible nucleoli inside the nucleus of a BCC elongated cell	Prominent nucleoli in the nucleus of keratinocytes
Subtotal (weight)	**1 (0.9)**		
Epidermal shadow[6,27]	2	Large featureless area with blurred border disrupting the normal epidermis and corresponding to the horizontal clefting	Not known, probably an optical effect of the en face view of an underlying tumor nest
Weighted subtotal*	**2 (1.9)**		
Ulceration[23,26]	2	Disruption in the bright skin surface and in the underlying layers of the epidermis, seen as a dark area with or without bright amorphous or fibrillar debris[12]	Ulceration of the epidermis
Weighted subtotal*	**2 (1.9)**		
Onion-like structures[23,26]	2	Round black spaces centered by brightly refractile material, corresponding to milia-like cysts	Epidermal cysts
Weighted subtotal*	**2 (1.9)**		
Weighted total for suprabasal epidermis	**27 (25.7)**		
Basal layer-DEJ-superficial dermis term (n = 45; 77.6%)			
Pigmented nests of basal cells[16]	1	Highly packed cells corresponding to islands of basaloid tumor cells with high refractivity	Nests of basaloid cells in the DEJ or superficial dermis, mostly associated with the nodular subtype
Tumor nodules[18,19]	2		
Nests of basaloid cells[21]	1		
Tumor island[22,25,26]	3		
Bright tumor islands[24]	1		
Small tumor islands[23]	1	Tumor islands <300-μm diameter	
Big tumor islands[23]	1	Tumor islands >300-μm diameter	
Weighted subtotal*	**10 (9.5)**		
Basaloid cells[17]	1	Cells with elongated nuclei and a palisading in the periphery of the tumor parenchyma	Organization of basaloid cells at the periphery of tumor nests
Palisading[18,22]	2		
Peripheral palisading[21,23-26]	5		
Weighted subtotal*	**8 (7.6)**		

Continued

Table I. Cont'd

RCM term	Use frequency of RCM term, n (%)	Definition	Histopathologic correlates
Peritumoral dark space[18]	1	Cleft-like hyporeflective spaces surrounding tumor nests	Clear spaces between the tumor parenchyma and surrounding stroma, most probably corresponding to mucin
Cleft-like spaces[20]	1		
Clefting[6,23,27]	3		
Clefts[43]	1		
Peripheral clefting[26]	1		
Dark peritumoral cleft[24,25]	2		
Weighted subtotal*	**9 (8.6)**		
Cord-like structures[18,26]	2	Tightly packed tumor cells forming trabeculae	Nests of basaloid cells connected to the DEJ, highly associated with the superficial subtype
Basaloid cords and nodules[6,27]	2		
Cord[23]	1		
Weighted subtotal*	**5 (4.7)**		
Dendritic structures[19]	1	Bright, thin, or coarse dendritic-like structures within tumor islands frequently associated with a clearly visible nucleated cell	When within tumor nests, they mostly correspond to melanocytes (melan-A stain) and few are Langerhans cell (CD1a)
Dendritic-like features[6]	1		
Nucleated cell within tumor island[6]	1		
Bright dendritic structures[19,24]	1		
Dendritic cells[26†]	1		
Bright round cells[24]	1		
Weighted subtotal*	**6 (5.7)**		
Dark silhouettes[22-26]	5	Low reflectance tumor islands, Longo[23]; hyporeflective areas outlined by bright collagen bundles in the surrounding dermis that correspond to basaloid islands	Nests of basaloid cells in the superficial dermis or deeper, not visible due to the lack of resolution after 150-200 μm. Associated with the infiltrative subtype
Dark nodules[26,27†]	1		
Weighted subtotal*	**6 (5.7)**		
Solar elastosis[21]	2	Peppelman et al;[21] bright irregular bundles and lace-like structures	Degeneration of the elastic fibers of the chronically sun-exposed skin
Weighted subtotal*	**2 (1.9)**		
Melanophages[16,18]	2	Irregularly shaped bright cells with ill-defined borders and usually no visible nucleus distributed within and outside tumor islands	Melanin-laden macrophages (melanophages) in the superficial dermis
Plump bright cells[19,21,22]	3		
Weighted subtotal*	**5 (4.7)**		
Collagen bundles[17]	1	Increased number of fiber bundles orientated parallel, surrounding tumor	Collagen reaction to the tumor in the surrounding stroma
Fibrosis surrounding tumor nests[21]	1		
Stromal reaction[26†]	1		
Thickened collagen bundles[24,25]	2		
Weighted subtotal*	**5 (4.7)**		
Increased vascularity[7,8,18,19,21-23,26]	8	Increased number of dilated (10-105 μm) blood vessels with occasional rolling of leukocytes (starting at 35—50-μm below epidermal surface); these vessels are often horizontal (parallel)	Dilated blood vessels running parallel to the epidermal surface
Enlarged blood vessels[17]	1		
Prominent vasculature[19]	1		
Linear telangiectasia—like horizontal vessels[6]	1		
Linear or convoluted dilated blood vessels[25,26]	2		
Linear blood vessels[24]	1		
Weighted subtotal*	**14 (13.3)**		
Fibrillar polarized pattern around tumor[6]	1	Fibrillary polarized features drawing a reticulation pattern around tumor island	NA
Weighted subtotal*	**1 (0.9)**		

Continued

Table I. Cont'd

RCM term	Use frequency of RCM term, n (%)	Definition	Histopathologic correlates
Inflammatory infiltrate[21]	1	Bright, highly refractile round or scattered cells representing leukocytes and neutrophils, respectively	Infiltrate of lymphocytes and leukocytes in the tumor parenchyma and stroma
Prominent inflammatory infiltrate[7,8,19]	3		
Inflammatory particles[26]	1		
Inflammation[23]	1		
Weighted subtotal*	**6 (5.7)**		
Total for basal layer-DEJ-superficial dermis terms	**78 (74.3)**		
Total for BCC terms (N = 58; 100%)	**105 (100)**		

Subtotals and totals are bolded.
BCC, Basal cell carcinoma; *DEJ*, dermoepidermal junction; *NA*, not applicable; *RCM*, reflectance confocal microscopy.
*Relative frequency of use of subgroup of terms; the denominator is the total times BCC terms were used in the literature (n = 105).
†Term has no definition in the cited articles; thus, grouping under each likely synonymous term was done by the authors of this paper.
‡The term was mentioned by the authors but not used.

if no agreement could be reach, a third author (Dr Scope) was consulted. The following information was extracted from each study: RCM terms, definition of the RCM terms, diagnosis associated with the terms, and (when known) the histopathologic correlate associated with that term. All extracted RCM terms were recorded as published in the literature, chronologically, in an Excel spreadsheet (Microsoft, Redmond, Washington). In addition, to weight the use frequency of RCM terms, we recorded the number of studies that used each term. Last, we identified all terms that were likely synonymous on the basis of them being associated with a similar RCM definition and histopathologic correlates (eg, cleft, clefting, and cleft-like space). Furthermore, terms were grouped by anatomic level of skin: a) suprabasal epidermis, including the corneal, granular, and spinous layers, and b) the epidermal basal layer, dermoepidermal junction (DEJ), and superficial dermis.

Summary measures and statistical analysis

Descriptive statistics were used to detail the number of RCM terms by diagnosis and anatomic layer. Use frequency describes the number of papers describing each RCM term. Weighted use frequency describes the relative use frequency for RCM terms per diagnosis: the use frequency for an RCM term (individual term or subgroups of synonymous terms) divided by the total use frequency for all terms describing that diagnosis.

RESULTS

Thirty-one studies met the inclusion criteria (Fig 1). We identified a total of 139 RCM terms for NMLs described in the literature, including 58 terms for diagnosis of BCC,[6-8,16-27] 58 terms for SCC and AK,[6,9,28-37] and 23 terms for SK/SL/LPLK.[10,31,38-42]

The use frequency of each RCM term and subgroups of likely synonymous RCM terms are shown by diagnosis (Tables I-III).[6-10,16-29,31-43] The overall average use frequency of RCM terms was 1.6 (range 1-8). When stratified by specific diagnosis, the average use frequency of RCM terms was 1.8 (range 1-8) times for the diagnosis of BCC, 1.6 (range 1-7) times for SCC and AK, and 1.4 (range 1-3) times for SK/SL/LPLK. For example, commonly used RCM terms included increased vascularity, used 8 times among BCC-related papers, and atypical honeycomb pattern, used 7 times across SCC-related articles. In contrast, the terms prominent nucleoli and fibrillar polarized pattern around tumor were used only once among BCC-related papers, and the term multinucleated keratinocytes was used only once across SCC-related articles.

By grouping of individual RCM terms on the basis of likely synonymous definition and histopathologic correlates, the total number of RCM terms could be reduced from 139 to 66 (52.5% reduction), including a 68.9% reduction (58 terms down to 18 terms) for BCC (Table I), 37.9% reduction (58 terms down to 36 terms) for SCC and AK (Table II), and 47.8% reduction (23 terms down to 12 terms) for SK/SL/LPLK (Table III).[6-10,16-29,31-43]

Weighted use frequency for each subgroup of likely synonymous RCM terms was analyzed by diagnosis. The most commonly used term subgroups for BCC (Table I) were streaming and polarization of nuclei (n = 15; 14.2%), increased vascularity and prominent vascularity (n = 14; 13.3%), and tumor nodules and bright tumor islands (n = 10; 9.5%).[6-8,16-27-43] The most commonly used term subgroups for

Table II. SCC RCM terms, frequency of use in the literature, and suggested grouping on the basis of similarity of definitions and histopathologic correlates

RCM term	Use frequency of RCM term, no (%)	Definition	Histopathologic correlates
Suprabasal epidermis term (n = 37; 63.7%)			
Hyperkeratosis[32,35,37]	3	Thickening of the stratum corneum >15 μm	Hyperkeratosis
Weighted subtotal*	**3 (3.2)**		
Parakeratosis[32,34-37]	5	Nucleated cells appearing as dark nuclei surrounded by bright outline of centrally stratum corneum corneocytes	Parakeratosis
Weighted subtotal*	**5 (5.3)**		
Detached corneocytes[32]	1	White, highly refractive polygonal structure of ~30-40 μm in diameter in the stratum corneum	Detached corneocytes
Polygonal nucleated cells at the stratum corneum[9]	1		
Disruption, individual cells[36]	1		
Individual corneocytes[37]	1		
Superficial epidermal disruption[33]	1		
Weighted subtotal*	**5 (5.3)**		
Stratum corneum disruption[37]	1	Alteration of the smooth contour of the stratum corneum observed in mosaic images	NA
Weighted subtotal*	**1 (1.1)**		
Orthokeratosis[32]	1	Hyperkeratosis without parakeratosis	Orthokeratosis
Weighted subtotal*	**1 (1.1)**		
Scale[9,34,36]	3	Variably refractile, amorphous material in stratum corneum	Hyperkeratosis
Weighted subtotal*	**3 (3.2)**		
Atypical honeycomb pattern[6,9,31-33,35,36†]	7	Irregularly shaped cells deviating from the normal honeycomb pattern	Variation in cellular and nuclear shape and size of epidermal keratinocytes
Diamond-shaped honeycomb[6]	1		
Irregular honeycomb pattern[29,34]	2		
Weighted subtotal*	**10 (10.7)**		
Architectural disarray[28,32]	2	Severe disarranged epidermal pattern in which the honeycomb pattern is no longer visible	Severe variation in cellular and nuclear shape and size of epidermal keratinocytes
Honeycomb atypical and disarrayed[6]	1		
Loss of regular stratification of epidermal layers[29]	1		
Disarranged epidermal pattern[9,31,36]	3		
Architectural disarrangement[35,37]	2		
Weighted subtotal*	**9 (9.6)**		
Cellular and nuclear pleomorphism (of the epidermis)[32]	1	Variation in cellular and nuclear shape and size (refers to the individual cellular morphology more than an epidermal pattern)	Variation in cellular and nuclear shape and size
Different size and shape of nuclei of keratinocytes[29]	1		
Keratinocyte pleomorphism[37]	1		
Pleomorphic nuclei of keratinocytes[28]	1		
Weighted subtotal*	**4 (4.3)**		
Irregular borders of keratinocytes[29]	1	Irregular borders of keratinocytes	NA
Weighted subtotal*	**1 (1.1)**		
Irregular intercellular keratinocyte connections[29]	1	Irregular intercellular keratinocyte connections	NA
Weighted subtotal*	**1 (1.1)**		

Continued

Table II. Cont'd

RCM term	Use frequency of RCM term, no (%)	Definition	Histopathologic correlates
Targetoid cells[32,33,35,36‡]	4	2 cell types have been described: large cell with a bright center and dark peripheral halo (denoted as targetoid cells 1)[32,33] and large cell with a dark center and bright rim surrounded by a dark halo (denoted as targetoid cells 2)[32,33]	Dyskeratotic keratinocytes within the epidermis
Dyskeratotic areas[29]	1		
Round nucleated cells at spinous-granular layer[9]	1		
Dyskeratotic cell[28]	1		
Weighted subtotal*	**7 (7.5)**		
Multinucleated keratinocytes[32]	1	Large cells with tight aggregates of bright nuclei	Multinucleated keratinocytes
Large cells with aggregated nuclei in epidermis[33]	1		
Weighted subtotal*	**2 (2.1)**		
Spongiosis[32,35]	2	Enlargement of the bright intercellular spaces due to fluid accumulation between keratinocytes	Spongiosis
Weighted subtotal*	**2 (2.1)**		
Exocytosis[32]	1	Inflammatory cells appearing as highly refractive structures in epidermis	Exocytosis
Weighted subtotal*	**1 (1.1)**		
Spindle-shaped cells with dendritic branches infiltrating the epidermis[34]	1	Bright cells with elongated branching structures extending from fusiform cell body; seen at the spinous and granular layers of the epidermis (corresponding to Langerhans cells of pigmented SCC or pigmented AK)	Langerhans cells infiltrating the epidermis
Dendritic cells in the epidermis[35,36§]	2		
Weighted subtotal*	**2 (2.1)**		
Erosion, ulceration[35]	1	Dark areas with sharp borders and irregular contours filled with amorphous material, cellular debris, and small particles	Ulceration of the epidermis
Weighted subtotal*	**1 (1.1)**		
Corneal pseudocysts[36]	1	Well-circumscribed large, round, highly refractile intraepidermal structures	Intraepidermal cysts
Weighted subtotal*	**1 (1.1)**		
Speckled nucleated cells in the epidermis[35]	1	Roundish-to-polygonal cells with speckled appearance and dark nucleus in epidermis, size slightly larger than surrounding keratinocytes, they are larger than lymphocytes and have a polygonal shape that differentiates them from dendritic cells	NA
Weighted subtotal*	**1 (1.1)**		
Weighted total for suprabasal epidermis	**60 (64.5)**		
Basal layer-DEJ-superficial dermis terms (n = 21; 36.2%)			
Elongated dermal papillae[28]	1	Elongated dermal papillae	NA
Weighted subtotal*	**1 (1.1)**		
Edged papillae[34]	1	Multiple scattered dermal papillae demarcated by rim of bright cells; in pigmented SCC, the edged papillae are mostly peripheral in location with widened interpapillary spaces	Atypical pigmented keratinocytes
Weighted subtotal*	**1 (1.1)**		

Continued

Table II. Cont'd

RCM term	Use frequency of RCM term, no (%)	Definition	Histopathologic correlates
Mottled pigmentation[36§]	1	Corresponds to presence of clustered, bright keratinocytes detectable in context of honeycombed pattern	Basilar pigmented keratinocytes
Weighted subtotal*	**1 (1.1)**		
Keratin pearl[32,35]	2	Whorl-shaped accumulation of keratin, appearing as highly refractive, speckled structure in the dermis[¶]	Keratinization
Weighted subtotal*	**2 (2.1)**		
Convoluted glomerular vessel[6]	1	Coiled canalicular vessels	Aberrant vessels
Weighted subtotal*	**1 (1.1)**		
Linear vessels[36]	1	Vessels oriented parallel to imaging plane	Aberrant vessels
Weighted subtotal*	**1 (1.1)**		
Round blood vessels traversing the dermal papilla[9,36]	2	Dilated blood vessels within the dermal papillae that run perpendicular to the horizontal RCM plane of imaging, dilated blood vessels within the dermal papillae looping perpendicular to the horizontal plane of RCM imaging, presence of multiple looping vessels renders the dermal papillae a button-hole–like appearance	Aberrant and neo formed vessels
Round-to-oval vessels[33]	1		
Buttonhole vessels[35,36]	2		
Dilated looping blood vessels withinpapillae[34,35]	2		
Weighted subtotal*	**7 (7.5)**		
Increased number of blood vessels[32,37]	2	>5 blood vessels per 0.5 × 0.5 mm	Neovascularization
Weighted subtotal*	**2 (2.1)**		
Increased blood vessel dilatation[32,37]	2	Blood vessels of diameter >5 μm	Aberrant vessels
Weighted subtotal*	**2 (2.1)**		
S-shaped vessels[33]	1	Round-to-oval vessels with increased tortuosity at center of dermal papillae, S-shaped at lower papillary dermis	NA
Weighted subtotal*	**1 (1.1)**		
Solar elastosis[32,37]	2	Network of thick, highly refractile collagen bundles intermixed with moderately refractive, lace-like elastic fibers	Solar elastosis
Curled fibers[36]	1		
Weighted subtotal*	**3 (3.2)**		
Huddled collagen bundles[36]	1	Large hyporefractive blotches of amorphous and hyporeflective material, individual collagen fibers are no longer visible	NA
Weighted subtotal*	**1 (1.1)**		
Coarse collagen bundles[36]	1	Bright fibrillar structures that appear finely reticulated, forming a web-like structure	NA
Weighted subtotal*	**1 (1.1)**		
Nest-like structures[32,35]	2	Round, demarcated structures in the dermis that are often surrounded by fibrosis	NA
Weighted subtotal*	**2 (2.1)**		
Plump cells[34-36]	3	Irregularly shaped bright cells with ill-defined borders and usually no visible nucleus distributed within and outside tumor islands	Melanin-laden macrophages (melanophages) in dermis
Weighted subtotal*	**3 (3.2)**		

Continued

Table II. Cont'd

RCM term	Use frequency of RCM term, no (%)	Definition	Histopathologic correlates
Speckled nucleated cells in the dermis[35]	1	Roundish to polygonal cells with speckled appearance and dark nucleus within the dermis, they are larger than the usual size of lymphocytes and have a polygonal shape that differentiate them from plump bright cells	NA
Weighted subtotal*	**1 (1.1)**		
Inflammatory cells[32,33,37]	3	Highly refractile structures of 8-10 μm in diameter located in the epidermis or dermis	Inflammatory cells: lymphocytes and neutrophils
Weighted subtotal*	**3 (3.2)**		
Total for basal layer-DEJ-superficial dermis terms	**33 (35.4)**		
Total for SCC terms (N = 58)	**93 (100)**		

Subtotals and totals are bolded.

AK, Actinic keratosis; *DEJ*, dermoepidermal junction; *NA*, not applicable; *RCM*, reflectance confocal microscopy; *SCC*, squamous cell carcinoma.

*Relative frequency of use for subgroup of terms; the denominator is the total times SCC terms were used in the literature (n = 93).

†Most studies recommend stating partial-thickness or full-thickness atypia to differentiate between AK and SCC.

‡Term mainly described in association with Bowen disease.

§Features of pigmented AK.

¶This feature can also be seen in the epidermis.

SCC and AK (Table II) were atypical honeycomb pattern (n = 10; 10.7%), architectural disarray (n = 9; 9.6%), and dyskeratotic cells and buttonhole vessels (each, n = 7; 7.5%).[6,9,28,29,31-37] The most commonly used term subgroups for SK/SL/LPLK (Table II) were bulbous projections (n = 7; 21.2%), milia-like cysts (n = 4; 13.3%), typical honeycomb pattern (n = 4; 12.1%), presence of plump cells and melanophages (n = 4; 12.1%), and polycyclic dermal papillae (n = 4; 12.1%).

We also stratified RCM terms by anatomical level of skin, the suprabasal epidermis versus the epidermal basal layer, DEJ, and superficial dermis. For BCC, 13 (22.4%) individual RCM terms (in 6 synonymous term subgroups, 33.3%) referred to structures in the suprabasal epidermal layer, and 45 (77.5%) individual RCM terms (in 12 synonymous term subgroups, 66.6%) described features in the basal layer, DEJ, or superficial dermis. The weighted use frequency for basal layer-DEJ-superficial dermis terms (n = 78; 74.2%) was higher than that of suprabasal epidermis terms (n = 27; 25.7%).

For SCC and AK, 37 (63.7%) individual RCM terms (in 19 synonymous term subgroups, 51.3%) described features in the suprabasal epidermal layer, and 21 (36.2%) individual RCM terms (in 18 synonymous term subgroups, 48.6%) described features present in the basal layer, DEJ, or superficial dermis. The weighted use frequency for suprabasal epidermis terms (n = 60; 64.5%) was higher than that for basal layer-DEJ-superficial dermis terms (n = 33; 35.4%).

For SK/SL/LPLK, 9 (39.1%) individual RCM terms (in 6 synonymous term subgroups, 50%) referred to structures present in the suprabasal epidermal layer, and 14 (60.8%) individual RCM terms (in 6 synonymous term subgroups, 50%) described structures present in the basal layer, DEJ, or superficial dermis. The weighted use frequency for suprabasal epidermis terms (n = 15; 45.4%) was similar to that of basal layer-DEJ-superficial dermis terms (n = 18; 54.5%).

DISCUSSION

RCM is a noninvasive imaging technique that has demonstrated good clinical utility in the diagnosis, margin assessment, and treatment monitoring of skin neoplasms.[1,44] However, learning to read RCM images may be perceived, at present, as a daunting task that should be left in the hands of dedicated experts. The inconsistent use of RCM terminology in the literature and in scientific meetings probably poses a barrier to the adoption of RCM by novices. As RCM terminology is still evolving, a systematic review of the terms is warranted at this juncture.

Toward improving the consistency of RCM terminology use, we conducted a systematic review of terms for the diagnosis of common benign and malignant NMLs. The goal was to create a more

Table III. SL/SK/LPLK RCM terms, frequency of use in literature, and suggested grouping on the basis of similarity of definition and histopathological correlates

RCM term	Use frequency of RCM term, n (%)	Definition	Histopathologic correlates
Suprabasal epidermis term (n = 9; 39.1%)			
Milia-like cysts[31]	1	Homogeneous, bright areas without sharply demarcated borders surrounded by a dark halo within the epidermis	Intraepidermal keratin cysts
Corneal pseudo cysts[10,39,41]	3		
Weighted subtotal*	**4 (12.1)**		
Keratin-filled invaginations[10,41]	2	Round-to-longitudinal invaginations of the lesion surface, harboring structureless amorphous material of variable brightness on RCM	Keratin-filled papillomatous epidermis
Surface holes and fissures[39]	1		
Weighted subtotal*	**3 (9.1)**		
Cerebriform appearance[38]	1	Round-to-linear structures, darker than the surrounding epidermis, resembling the surface of a brain (gyri and sulci)	Papillomatous epidermis
Weighted subtotal*	**1 (3.03)**		
Typical honeycomb pattern[39]	1	Honeycomb pattern with regular thickness of lines and sizes of holes	Regular epidermis
Regular honeycomb pattern[10,41,42]	3		
Weighted subtotal*	**4 (12.1)**		
Epidermal projections[10,41]	2	Projections of the epidermal surface of the lesion	Projections of rete ridges
Weighted subtotal*	**2 (6.1)**		
Small, bright homogeneous cells[31†]	1	Small, bright homogeneous cells present on basal layers, corresponding to pigmented keratinocytes	Pigmented keratinocytes in the basal layer
Weighted subtotal*	**1 (3.03)**		
Total for suprabasal epidermis (weight)	**15 (45.4)**		
Basal layer-DEJ-superficial dermis term (n = 14; 60.8%)			
Polycyclic shapes of dermal papillae[38]	1	At the DEJ, densely packed round-to-polymorphous dermal papillae, usually with pigmented keratinocytes	Elongated and bridging rete ridges with pigmented keratinocytes
Densely packed round-to-polymorphous dermal papillae[10]	1		
Packed dermal papillae[41]	1		
Polycyclic papillary contours[40]	1		
Weighted subtotal*	**4 (12.1)**		
Edged papillae[42]	1	Dark round-to-oval structures surrounded by a rim of bright monomorphic cells	Pigmented keratinocytes at DEJ
Weighted subtotal*	**1 (3.03)**		
Cords[‡] and bulbous projections[10,41]	2	Elongated, bright tubular structures (cords[‡]) with bulbous projections at the DEJ	Elongated and bridging rete ridges with pigmented keratinocytes
Cord-like[‡] rete ridges[42]	1		
Elongated cords[39‡]	1		
Anastomosing epithelial cords[31‡]	1		
Bulbous projections[39]	1		
Weighted subtotal*	**7 (21.2)**		
Mixed vascular pattern[10,41]	2	Prominent vascular pattern with dilated round and linear blood vessels (running perpendicular and parallel, respectively)	Neovascularization
Weighted subtotal*	**2 (6.1)**		

Continued

Table III. Cont'd

RCM term	Use frequency of RCM term, n (%)	Definition	Histopathologic correlates
Plump bright cells[10,31,39§]	3	Irregularly shaped bright cells with ill-defined borders and no visible nucleus, corresponding to melanophages	Melanin-laded macrophages (melanophages) in the superficial dermis
Melanophages[10§]	1		
Weighted subtotal*	**4 (12.1)**		
Bright stellate spots[39‖]	1	Small, bright round structures (<20 μm) without visible nucleus corresponding to leukocytes	Inflammatory cells: lymphocytes and neutrophils
Weighted subtotal*	**1 (3.03)**		
Total for basal layer-DEJ-superficial dermis terms	**18 (54.5)**		
Total for SL/SK/LPLK terms (N = 23; 100%)	**33 (100)**		

Subtotals and totals are bolded.

DEJ, Dermoepidermal junction; *LPLK*, lichen planus–like keratosis; *RCM*, reflectance confocal microscopy; *SK*, seborrheic keratosis; *SL*, solar lentigo.

*Relative frequency of use for subgroup of terms; the denominator is the total times SL/SK/LPLK terms were used in the literature (n = 33).

†Despite not defined for this group of lesions, we recommend using the standard term cobblestone pattern to avoid confusion.

‡We do not recommend using the term cords to avoid confusion with cord-like structures of basal cell carcinoma.

§These criteria have been associated mostly with LPLK.

‖The term Inflammatory infiltrate was not used in the literature in reference to SL/SK/LPLK; for consistency with the LPLK/SK/SL published literature, we recommend using bright stellate spots.

concise and unified glossary of RCM terms for NMLs. First, we gathered all RCM terms described in pertinent original peer-reviewed papers and then identified likely synonymous terms that had similar definitions and histopathology correlates. We found a total of 139 RCM terms used to describe features of common NMLs in the literature—an overwhelming number for a novice to comprehend. By grouping on the basis of likely synonymy, the list of terms could be reduced by at least half. Furthermore, we assigned a relative weighted score for each RCM term by using its frequency of usage in the literature. We found an average use of 1.6 times for a given term across 31 studies, highlighting the inconsistent usage of RCM terms.

We also observed that the use frequency of terms was highest for the anatomic location where the neoplasm is expected to proliferate (the histopathologic correlate). For instance, most RCM terms (~75%) for BCC were used to describe features in the DEJ and superficial dermis, where BCC aggregates proliferate. Likewise, roughly two thirds (~65%) of the RCM terms for SCC and AK described features located in the epidermal layer, corresponding to the pertinent anatomic location of histopathologic diagnostic criteria for these neoplasms. This finding confirms at a larger scale (systematic review) the good correlation between histopathology and RCM. Farnetani et al found a higher interobserver reproducibility for epidermal layer RCM terms than dermal layer RCM terms[12]; they conjectured that the degrading RCM optical resolution and image quality with increasing imaging depth accounts for this observation.[12] Larger studies are needed to confirm these findings.

Toward generating a shortlist of most pertinent RCM terms, we propose several steps. First, redundant terms need to be unified, as suggested herein. Second, omission of most infrequently used terms (eg, prominent nucleoli and onion-like for BCC[7,23]) should be considered. Third, unified terms that have been assigned diagnostic value in studies (eg, tumor islands for BCC) should be ranked higher than descriptive, supportive terms (eg, presence of plump cells in the dermis and button-hole sign for SCC) without clear diagnostic utility. Last, for select RCM terms with clear-cut histopathologic correlates and future new terms, the histopathologic term could be preferred (eg, dyskeratotic cells instead of targetoid cells), facilitating communication between clinicians and dermatopathologists.

Our study has limitations. First, although the initial tier of our search did not impose any language restrictions, we only included full-text articles in English. This was done to enable direct comparisons of terms without biases due to translation. However, distinct RCM terms in non-English language papers could have been missed. Second, for standardization, all non–peer-reviewed articles such as book chapters, conference papers, and case reports were excluded; we could have missed some up-to-date terms coined by the experts, especially in book chapters. Third, the weightage given to the RCM terms in this review

might have been influenced by frequency of publications by a specific researcher or a group.

CONCLUSION

Through systematic review, we presented a glossary of RCM terms for the diagnosis of NMLs. By grouping the terms on the basis of likely synonymy of the associated definition and histopathologic correlation, the number of RCM terms published in the literature could be reduced by approximately 50%. This systematic review might form the basis for an expert Delphi consensus process on NML terminology. A concise reproducible glossary of RCM terms can facilitate learning and clinical application of RCM by dermatologists.

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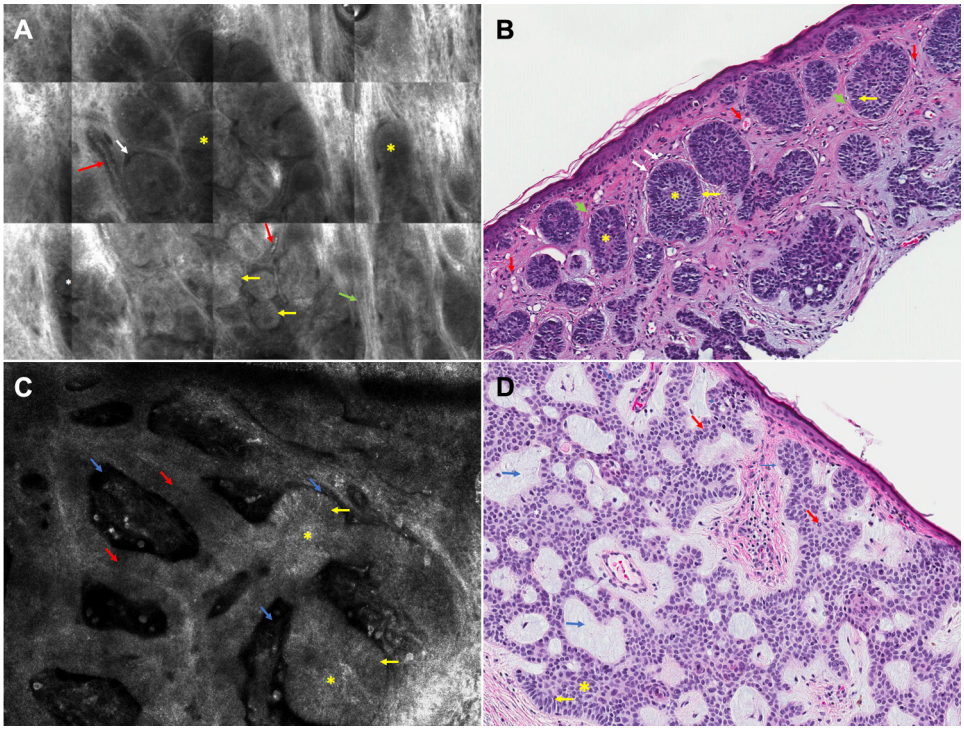
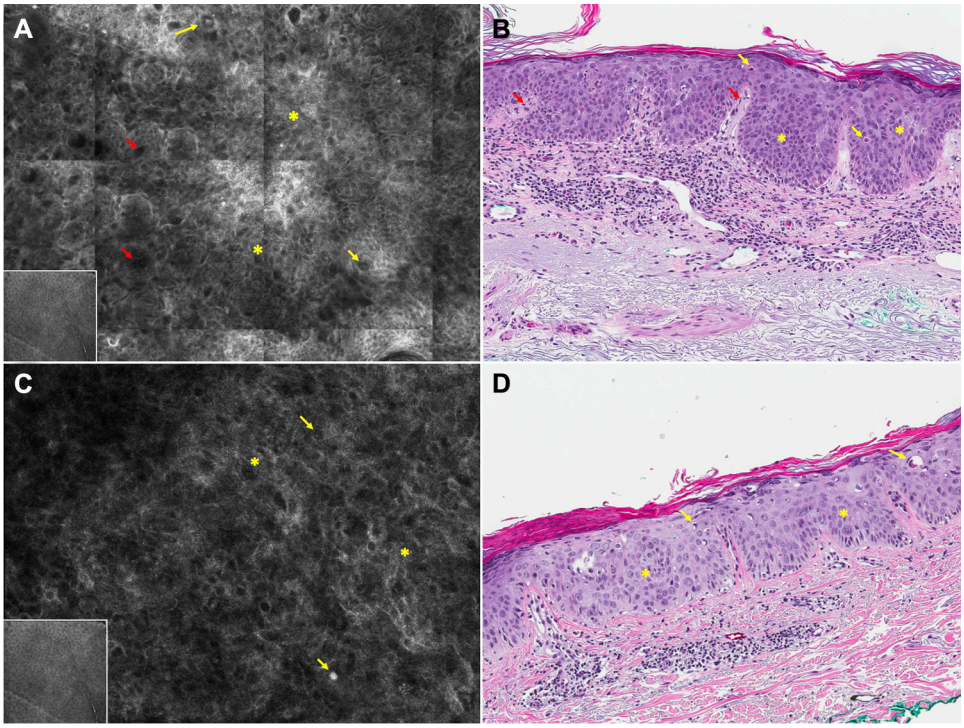
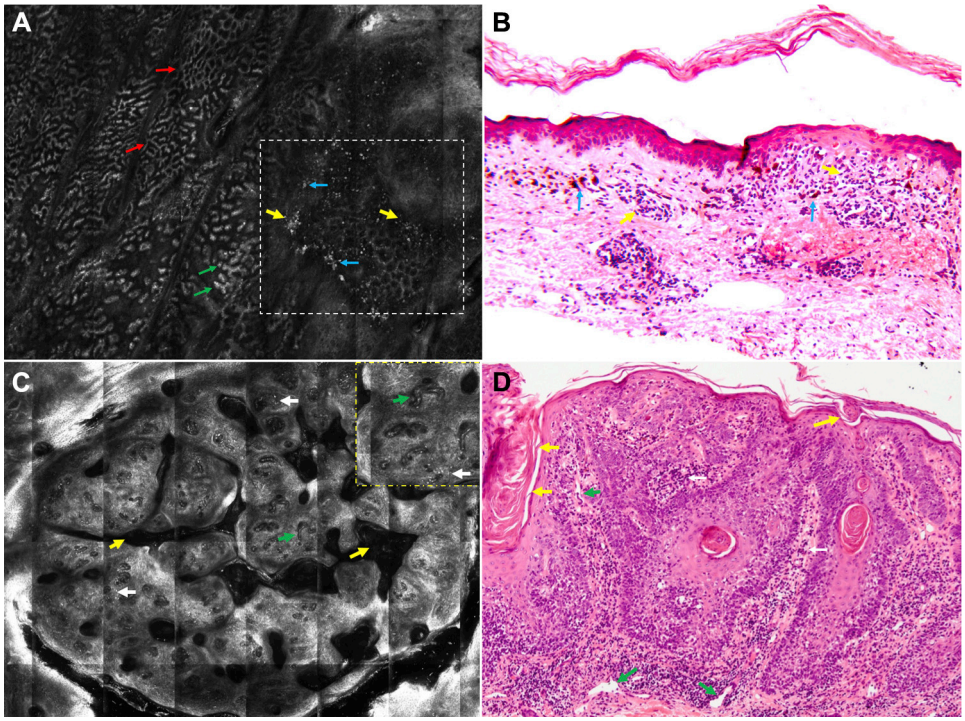


Supplemental Fig 1. Basal cell carcinoma (BCC)**. A,** RCM mosaic (1.7 x 1.5 mm), at the superficial dermis level, of a nodular BCC showing tumor islands (*yellow asterisks*) with palisading (*yellow arrows*) and clefting (*white arrows*). The surrounding stroma displays bright collagen bundles (*green arrows*). In addition, there are dilated vessels (*red arrows*) coursing parallel to the *en face* imaging plane. **B.** Corresponding histopathologic section showing basaloid neoplastic aggregates (*yellow asterisks*), with peripheral palisading and adjacent mucin-filled clefts (*white arrows*). There is fibroplasia (*green arrows*) and prominent vascularity (*red arrows*) in the surrounding stroma. (Hematoxylin-eosin stain; original magnification: X10.) **C,** RCM image (0.75 x 0.75 mm) of a superficial and nodular BCC showing cord-like tumor structures (*red arrows*) with palisading (*yellow arrows*) and clefting (*blue arrows*). There are also tumor islands (*yellow asterisks*). **D,** Corresponding histopathologic section showing anastomosing neoplastic aggregates (*red arrow*) which emanate from the undersurface of an atrophic epidermis. The neoplastic aggregates (*red arrows* and *yellow asterisk*) are immersed in a mucinous stroma (*blue arrows*). (Hematoxylin-eosin stain; original magnification: X10.)



Supplemental Fig 2. Squamous cell carcinoma in situ. **A.** RCM mosaic (3.0 x 2.0 mm) image at the spinous-granular/dermoepidermal junction layer showing atypical honeycomb pattern (*yellow asterisks*), dilated vessels looping the dermal papillae (so called "buttonhole vessels"; *red arrows*), and bright dyskeratotic cells (*yellow arrows*). The insert is showing a regular honeycomb pattern of normal skin to compare. **B.** Corresponding histopathologic section showing a full-thickness epidermal atypia (*yellow asterisks*) with crowding, pleomorphism, and disarray of nuclei and with dyskeratotic cells (*yellow arrows*). In addition, there are tortuous looping blood vessels traversing the dermal papillae (*red arrows*). (Hematoxylin-eosin stain; original magnification: X10.) **C,** RCM image (0.75 x 0.75 mm) at the spinous-granular layer showing disarranged honeycomb pattern (*yellow asterisks*) and bright dyskeratotic cells (*yellow arrows*). The insert is showing a regular honeycomb pattern of normal skin to compare. **D,** Corresponding histopathologic section showing full-thickness epidermal atypia with nuclear pleomorphism (*yellow asterisk*) and dyskeratotic cells (*yellow arrows*). (Hematoxylin-eosin stain; original magnification: X20.)



Supplemental Fig 3. Solar lentigo/lichen planus-like keratosis (LPLK)/seborrheic keratosis. **A,** RCM mosaic (2.5 x 2.5 mm), at the dermoepidermal-junction, showing polycyclic dermal papillae *(red arrows*) and bulbous projections (*green arrows*) of a solar lentigo on the left side of the image and inflammatory infiltrate composed of plump bright cells (*blue arrows*) and small bright cells (*yellow arrows*) of a LPLK on the right-side of the image (*white dashed square area*). **B,** Corresponding histopathologic section (from the dashed square on panel **A** on RCM) shows the area of lichen planus-like keratosis with inflammatory infiltrate composed of melanophages (*blue arrows*) and lymphocytes (*yellow arrows*). (Hematoxylin-eosin stain; original magnification: X20.) **C,** RCM mosaic (3.0 x 3.5 mm), at the suprabasal epidermis layer, of a seborrheic keratosis showing keratin plugs and crypts (*yellow arrows*), C- and S-shaped vessels (*green arrows*), and inflammatory infiltrate (*white arrows*). **D,** Corresponding histopathologic section (from the dashed square on panel **C** on RCM**)** shows an inflamed seborrheic keratosis with keratin plugs (*yellow arrows*), dilated vessels (*green arrows*), and lymphocytes (*white arrows*). (Hematoxylin-eosin stain; original magnification: X20.)