REVIEW

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

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

Objective: To review published RCM terms for melanocytic lesions and identify redundant, synonymous terms.

Methods: A systematic review of original research articles adhering to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines was conducted until August 15, 2018. Two investigators gathered all published RCM terms used to describe melanoma and melanocytic nevi. Synonymous terms were grouped based on similarity in definition and in histopathologic correlation.

Results: Out of 156 full-text screened articles, 59 studies met the inclusion criteria. We identified 209 terms; 191 (91.4%) corresponding to high-magnification/cellular-level terms and 18 (8.6%) corresponding to low-magnification/architectural patterns terms. The overall average use frequency of RCM terms was 3.1 times (range, 1-31). By grouping of individual RCM terms based on likely synonymous definitions and by eliminating terms lacking clear definition, the total number of RCM terms could be potentially reduced from 209 to 40 terms (80.8% reduction).

Limitations: Non-English and non−peer-reviewed articles were excluded.

Conclusions: This systematic review of published RCM terms identified significant terminology redundancy. It provides the basis for subsequent terminology consensus on melanocytic neoplasms. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2020.05.097.)

Key words: diagnosis; melanocytic; melanoma; nevus; noninvasive; reflectance confocal microscopy; systematic review.

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Funding sources: Supported in part by a grant from the National Cancer Institute/National Institutes of Health (P30-CA008748) made to the Memorial Sloan-Kettering Cancer Center. Dr Scope's reflectance confocal microscopy research is funded by the Israel Science Foundation (ISF-1546-16).

Disclosure: Dr Halpern is a paid consultant for Canfield Scientific, Inc., is on the advisory board for SciBase, and was on the advisory board for Caliber ID. Drs Navarrete-Dechent, Liopyris, Monnier, and Aleissa; Authors Boyce and Oliviero; and Drs Rabinovitz, Marghoob, Pellacani, Scope, and Jain have no conflicts of interest to declare.

IRB approval status: Reviewed and approved by Memorial Sloan Kettering Cancer Center (#17-083).

Accepted for publication May 19, 2020.

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Published online July 31, 2020.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.05.097

Reflectance confocal microscopy (RCM) allows for noninvasive in vivo visualization of the skin at a quasi-histological resolution.[1] In the 1990s, the histologic correlates of RCM attributes of skin were first described.[2,3] Since then, numerous publications have shown the utility of RCM in the diagnosis of melanoma[4-7] and nonmelanoma skin cancer,[8-10] in the monitoring of noninvasive skin treatments,[11,12] and in guiding dermatologic surgery.[13-16]

As shown in a previous systematic review,[17] RCM terminology in the literature lacks consistency and contains many redundant terms. We identified a total of 139 RCM terms used to describe nonmelanocytic lesions (NMLs); by grouping these terms for synonymy, we were able to further shorten the list of terms by more than 50%.[17] For melanocytic lesions, a consensus study of RCM terminology was published in 2007 by Scope et al;[18] however, a multitude of new RCM terms, describing melanocytic neoplasms, have been published since.

Recently, category I Current Procedural Terminology reimbursement codes have been allotted to RCM imaging in the United States[1,19]; we anticipate a consequent rise in the integration of RCM into clinical practice.[20] To that end, there is a pressing need for standardization of RCM terminology of melanocytic lesions[17,21]—to enable structured reporting of RCM examinations and to facilitate RCM teaching to novices. Here, we performed a systematic review of the terms used to describe the RCM features of melanocytic neoplasms and identified redundant, synonymous terms.

CAPSULE SUMMARY

- Reflectance confocal microscopy (RCM) melanocytic neoplasms terminology is inconsistently used. Via systematic review, we identified redundant terms and categorized 209 synonymous terms into 40 groups (80.8% reduction).
- The proposed shortened list of RCM terms for melanocytic neoplasms may be easier to teach to novices and provides the basis for subsequent terminology consensus.

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 Systematic Reviews and Meta-analyses (PRISMA) statement (available at www.prisma-statement.org). All images used for illustrating RCM terms were acquired by using a commercial RCM system (Vivascope 1500 or Vivascope 3000, Caliber ID, Rochester, NY), under an institutional review board protocol (no. 17-083). The principles of RCM imaging have been previously described.[1]

Eligibility criteria

We included all original, peer-reviewed RCM articles published between 1995 and 2018 that contained the diagnosis of nevi, including congenital and Spitz nevi, and cutaneous melanoma. So-called borderline melanocytic lesions, such as atypical Spitzoid tumors, were also included. We excluded articles describing RCM features of collision tumors and melanocytic lesions of special anatomic sites, such as genitalia, nails, and eyelids. Literature reviews, single case reports, conference abstracts, animal studies, and publications lacking full text were excluded; because of the lack of peer-review process, we also excluded book chapters.

Information sources, search, and study selection

Systematic literature searches were conducted (August 15, 2018) in 4 databases with no specified date, age, sex, or language restrictions. The databases searched were 1) MEDLINE (via PubMed), 2) Embase, 3) The Cochrane Library (Cochrane), and 4) Web of Science. In an effort to be comprehensive and include gray literature publications into the data set of citations, conference proceedings and abstracts were retrieved from Embase and Web of Science by using broad and inclusive publication-type filters. Search results were combined in a bibliographic management tool (EndNote, Clarivate Analytics), and duplicates were eliminated both electronically and manually to ensure an efficient de-duplication process. The search strategy employed the Medical Subject Headings phrases: [“Microscopy, Confocal”] AND [“Skin Neoplasms” OR “Dermatology” OR “melanoma” OR “nevus” AND “in vivo”] AND [“Terminology” OR “Current Procedural Terminology” OR “Terminology as Topic” OR “Dictionaries as Topic” OR “Data Accuracy” OR “Algorithms” OR “Reproducibility of Results” OR “Classification”]. Bibliographies within retrieved articles were also reviewed to identify additional studies. For this specific systematic review, we included only RCM terms pertinent for melanocytic lesions and excluded terms related to nonmelanocytic neoplasms (eg, basal cell carcinoma, squamous cell carcinoma, and lichen planus–like keratosis). Two authors (CN-D and KL) independently screened all relevant titles and abstracts for eligibility. If

Abbreviations used:

DEJ: dermoepidermal junction
NML: nonmelanocytic lesion
RCM: reflective confocal microscopy

necessary, full-text articles were screened. Differences in judgment were resolved with a third reviewer (MJ) until consensus was achieved (Fig 1).

Data collection and extraction process

Two authors (CN-D and KL) extracted data from the included studies independently. Disagreements were resolved by consensus; if agreement could not be reached, a third author (MJ) was used as referee. The following information was extracted from each study: the RCM term, its definition, the diagnosis associated with the term, the histopathologic correlates associated with that term (when reported), and whether the term was used in an algorithm. All extracted RCM terms were recorded as published in the literature, chronologically, in an Excel spreadsheet (Microsoft, Redmond, WA). To weight the use frequency of RCM terms, we recorded the number of studies that used each term. Finally, 5 authors (CN-D, KL, JM, SA, and MJ) grouped all terms into likely synonymous terms based on their RCM definitions and on similar histopathologic correlates (eg, "pagetosis," "pagetoid infiltration," and "atypical cells in the epidermis"). Next, the likely synonymous RCM terms were organized by the skin layer to which they had been ascribed: 1) epidermis, 2) dermoepidermal junction (DEJ), and 3) dermis. Finally, we categorized all likely synonymous RCM terms into 2 categories: 1) high-magnification, cellular-level terms (based on optical sections, typically 0.5 × 0.5 μm to 1 × 1 mm in area) (eg, atypical cells, inflammatory infiltrate) and 2) low-magnification patterns (based on mosaic RCM images, typically >1 × 1 mm to 8 × 8 mm in area) (eg, ringed, meshwork, or clod pattern). RCM terms lacking definition in the main text, tables, or figures of an article (or where the definition could not be clearly inferred by the name of the term) were listed as "definition not available (N/A)." Additionally, following a previously published approach for simplifying terminology,[22] we extracted basic terminology units from composite terms (eg, the term "large roundish cells in the epidermis" contains the basic units "cells," "large," "roundish," and "epidermis"). *Composite terms* were defined as those that contained 2 or more basic units, and *simple terms* were those with a single unit. We then categorized the basic elements into "cells/structure" (the cell type could be explicit or implied by the term; eg, "cells" in the aforementioned example implies melanocytes), "morphologic descriptors/modifiers" (eg, "large" and "roundish"), and "anatomic location/distribution (eg, "epidermis").

Summary measures and statistical analysis

Descriptive statistics were used to categorize the number of RCM terms by diagnosis and by anatomic layer. *Use frequency* was based on the number of papers describing each RCM term. *Average use frequency* described the proportion between the use frequency for RCM terms (as individual terms or as subgroups of likely synonymous terms) divided by the total use frequency for all terms describing that diagnosis.

RESULTS

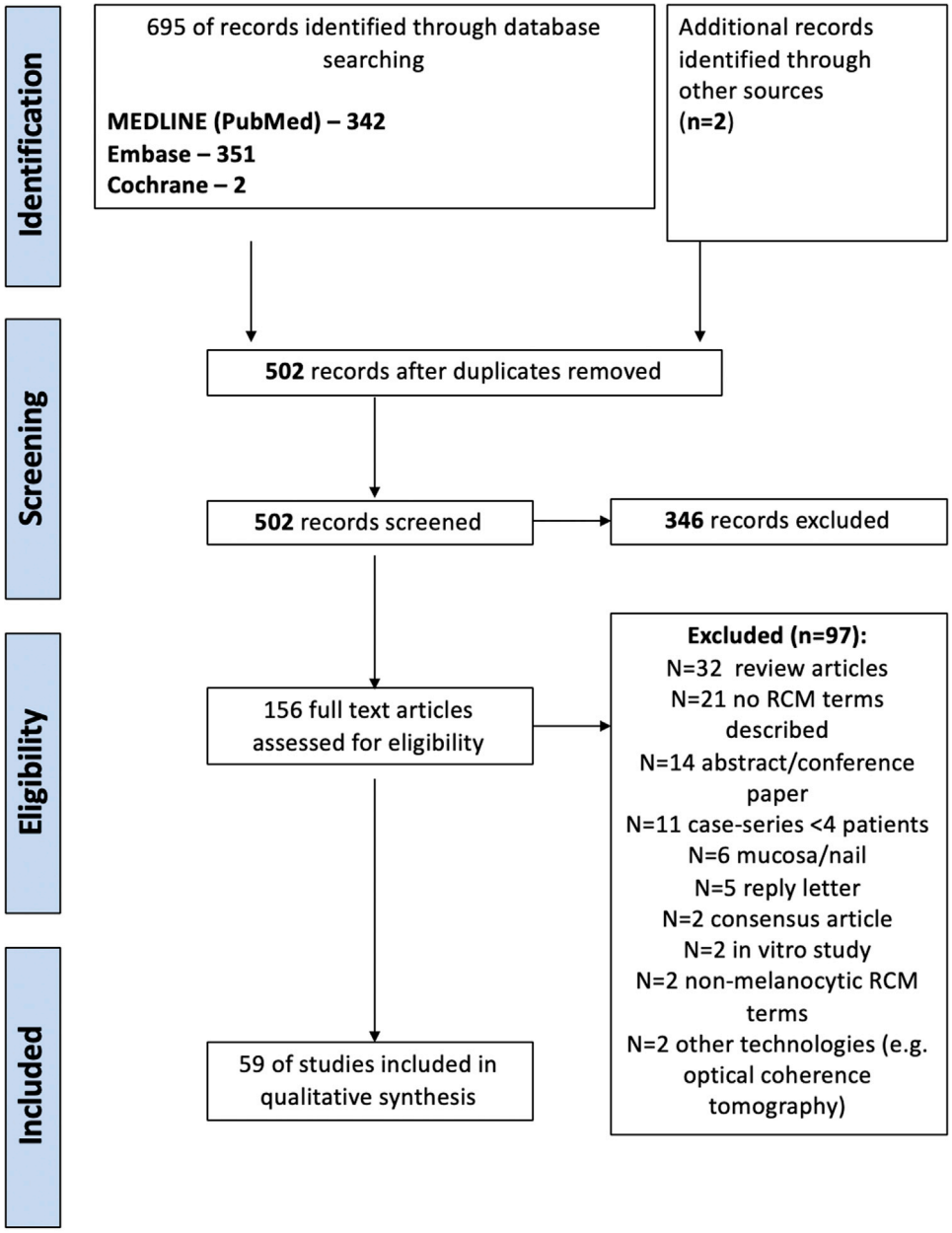
After screening 156 full-text articles, 59 studies were identified that met the inclusion criteria (Fig 1).[4-6,23-78] In total, 209 RCM terms were identified: 191 (91.4%) high-magnification/cellular-level terms and 18 (8.6%) low-magnification/architectural pattern terms. The use frequency of each individual RCM term and likely synonymous groups of RCM terms are shown in Tables I and II. Representative images for each category are also shown (Fig 2).

The overall average use frequency of the RCM terms was 3.1 times (653 mentions of 210 terms; range, 1-31 mentions). For high-magnification terms, the average use frequency was 3.0 times (591 mentions of 191 terms; range, 1-31), and for low-magnification terms, the average use frequency was 3.4 times (62 mentions of 18 terms; range, 1-18). The most commonly used high-magnification terms were "nonedged papillae" (use frequency, n = 31), "pagetoid cells" (n = 27), and "edged papillae" (n = 22). Only 14 (7.3%) were used in an algorithm (Table I). Among low-magnification terms, most frequently used were "meshwork pattern" (n = 16), "ringed pattern" (n = 15), and "clod pattern" (n = 10) (Table II).

We grouped terms on the basis of similarity in definitions and found 40 likely synonymous clusters. By further excluding 12 terms lacking a clear definition, the total number of terms could be reduced from 209 to 40 (80.8% reduction) (Table I).

High-magnification/cellular-level resolution terms

Among 191 high-magnification terms, 182 terms had an identifiable definition and could be grouped into 32 likely synonymous clusters. Nine additional



Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram. *RCM,* Reflectance confocal microscopy.

terms (6.6%) lacked a clear definition and were excluded from the likely synonymous clustering and from further analysis.

When stratifying the 182 individual high-magnification terms by their anatomic distribution, 68 terms mapped to the epidermis (37.4%), 46 terms to DEJ (23.9%), and 68 terms to the dermis (32.8%). When stratifying high-magnification terms by likely synonymous groups, 13 terms (40.6%) mapped to the epidermis, 11 (34.3%) to the DEJ, and 8 (25.0%) to the superficial dermis.

Of 182 terms, 52 (28.5%) were simple terms, and 130 (71.4%) were composite terms. We extracted 125 basic terminology units, 57 labeling the cell/structure type, 51 describing the morphologic attributes of these cells, and 17 relating to their anatomic distribution. We found that the 55 cells/structure terminology units could be categorized into 8 recurring

Table I. Reflectance confocal microscopy terms used to describe melanocytic lesions at high magnification, cellular-level resolution

RCM term	Use frequency of RCM term, n	Definition	Part of an algorithm	Histopathologic correlates
Epidermis (n = 68; 35.4%)				
Terms describing the presence of cells in the epidermis, using "pagetoid" without a specified cell shape				
Pagetoid cells[4,6,23,28-30,35,39,41,42,48,49,52,55,58,61,63-68,72,75-78]	27	Large nucleated cells, twice the size of keratinocytes (>20 um), with a dark nucleus and bright cytoplasm	Borsari et al, 2018[25]; Pellacani et al, 2007[68]	Presence of melanocytes in suprabasal layers of the epidermis
Pagetoid spread[25,32,33,56-58,60,62,75]	9			
Widespread pagetoid infiltration[4,6,36,37,43,53,58,59,68]	9			
Pagetoid melanocytes[44,54]	2			
Cells in pagetoid pattern[70]	1			
Pagetoid spread of atypical melanocytes[27]	1			
Irregular intraepidermal growth of melanocytes at the periphery of the lesion[32]	1			
Terms describing the presence of cells in the epidermis, specifying "pleomorphic" (round and dendritic) shape				
Polymorphic melanocytic cells[45-47]	3	Variability of the aspect of pagetoid cells (round and dendritic)		
Pleomorphic pagetoid infiltration[68]	1			
Pleomorphic pagetoid cells[23]	1			
Pleomorphic pagetoid shape[56]	1			
Pleomorphism (in the epidermis)[72]	1			
Bright dendrites/dendritic/round cells within the epidermis[64]	1			
Striking pleomorphism[49]	1			
Terms describing the presence of cells in the epidermis, specifying "round" shape				
Roundish pagetoid cells[36,37,49,56,59,68,72,74,75]	9	Large roundish nucleated cells, with a dark nucleus and bright cytoplasm, within suprabasal layers	Pellacani et al, 2007[68]; Segura et al, 2009[23]; Guitera et al, 2010[4]	
Round pagetoid cells[4,6,52,53,57,58]	6			
Round cells[5,38,57]	3			
Large roundish cells in the epidermis[34]	1			
Round pagetoid cells with halo[4,*]	1			
Terms describing the presence of cells in the epidermis, specifying "dendritic" shape				
Dendritic pagetoid cells[4,6,49,50,52,56,58,68,72,74,75]	11	Bright nucleated cells with dendritic-like branches within suprabasal layers		
Dendritic cells[5,38,55,57]	4	—		
Large dendritic cells in the epidermis[34]	1	—		
Terms describing the presence of cells in the epidermis, specifying "low refractivity"				
Hyporeflective pagetoid cells[77,78]	2	Round dark structures (similar to holes) within the epidermis		
Dark pagetoid cells[52,*]	1	—		
Terms describing the presence of "atypical/irregular" cells in the epidermis without a specific shape				
Cell atypia[6,52,58]	3	—		
Atypical cells[24,69]	2	—		
Enlarged atypical melanocytes[32]	1	—		
Irregularly bright melanocytic cells[46]	1	—		

Continued

Table I. Cont'd

RCM term	Use frequency of RCM term, n	Definition	Part of an algorithm	Histopathologic correlates
Weighted subtotal	**105**			
Terms describing the presence of dendrites in the epidermis				
Composite branching dendrites[37,46,47,55]	4	Numerous bright tangled lines within the epidermal layers, originating from dendritic cells, with cell body not always visible		Dendritic projections of melanocytes or Langerhans cells in the epidermis
Simple branching dendrites[46,47]	2			
Bright dendrites/tangled lines/dendritic cells[64]	1			
Dendritic structures[26]	1			
Dendritic processes[26]	1			
Frequent, coarse, branching dendrites[54]	1			
Weighted subtotal	**10**			
Terms describing the presence of melanocyte infiltration of hair follicles				
Follicular localization of pagetoid cells and/or atypical cells[4,29,34,61]	4	Infiltration of dendritic/roundish cells in the inner portion of the hair follicle or elongated protrusions around the entire perimeter of the follicle	Guitera et al, 2010[4]	Infiltration of hair follicles and adnexal structures by atypical melanocytes; typically seen in melanoma of the lentigo maligna type
Pagetoid cells around follicular opening[6,52,58]	3			
Folliculotropism[24,64]	2			
Atypical melanocytes surrounding adnexal openings[26]	1			
Infiltration of adnexal structures[27]	1			
Irregular aggregates of bright perifollicular cells[31]	1			
Atypical cells infiltrating follicular structures[62]	1			
Weighted subtotal	**13**			
Terms describing the presence of a normal/regular spinous and granular layer				
Honeycombed pattern (typical/regular)[4,23,38,39,43,49,55-57,63,65,66,68,75]	14	Well-demarcated cellular outlines of keratinocytes forming a grid-like structure resembling a honeycomb in the spinous and granular layers		Normal epidermal keratinocytes
Readily detected keratinocyte cell borders[45-47]	3			
Regular epidermal pattern[67]	1			
Terms describing the presence of a normal/regular basal layer				
Cobblestone pattern[4,23,38,39,42,43,49,57,58,63,65,66,68,69,72,74,75,77]	18	In the basal layer aggregates of small, nonnucleated polygonal cells and bright cytoplasm can be seen creating a cobblestone pattern		
Monomorphic melanocytic cells[45-47]	3			
Cobblestone with small nucleated cells[72,74]	2			
Typical cells in the basal layer[28,36]	2			
Homogeneous bright melanocytic cells[46]	1			
Monomorphic refractile cells[55]	1			
Typical basal cells[23]	1		Segura et al, 2009[23]	
Weighted subtotal	**46**			
Terms related to acanthosis of the epidermis				
Broadened honeycomb pattern[4,23,58,61,69,72,74,75]	7	Prominent bright epidermis intermingled with papillae		Acanthosis of the epidermis
Acanthosis[49]	1			
Weighted subtotal	**8**			
Terms describing the presence of atypical keratinocytes/disarrangement of keratinocytes				

Epidermal disarray[4,6,23,27,50,52,55,58,68]	9	Irregularly shaped keratinocytes with poorly defined or absent borders	Atypical keratinocytes with variation in size, shape, and crowding of the nuclei
Atypical honeycomb[58,68,69,72,74,77]	6		
Disarranged epidermis[57,67,69,72,75]	5		
Disarray[38,56,65,66]	4		
Disarranged epidermal pattern[43,63,67]	3		
Poorly defined or absent keratinocyte cell borders[45-47]	3		
Irregular epidermal pattern[67]	1		
Honeycomb atypical and disarray[52]	1		
Irregularly shaped keratinocytes[43]	1		
Poorly defined keratinocyte cell border[54]	1		
Loss of keratinocyte cellular borders[54]	1		
Honeycombed and irregular keratinocytes[64]	1		
Epidermal disruption[49]	1		
Weighted subtotal	**37**		
Terms related to a "speckled" appearance in the epidermis			
Grainy image[54,55,68,72]	4	Bright, granular, dust-like particles barely discernible as individual granules at the level of the epidermis	Extracellular melanin granules in the epidermis
Epidermal granularity[57]	1		
Weighted subtotal	**5**		
Dermoepidermal junction (n = 46; 23.9%)			
Terms associated with irregular papillary contours			
Nonedged papillae[4,6,23,29,31,33,36,37,39-41,43,48,49,52,53,57-59,61,63,65,67-70,72,74-77]	31	Dermal papillae without a demarcating bright rim of cells; the interpapillary areas of the epidermis are widened and often show large atypical melanocytes	Pellacani et al, 2007[68]; Guitera et al, 2010[4] Disarranged rete ridges with a disorderly proliferation of melanocytes not confined to the sides and tips of the rete ridges Loss of the papillary contour is associated with flattening of the DEJ
Irregular ringed[30]	1		
Terms associated with loss of papillae contours			
Nonvisible dermal papillae[4,50,58,75]	4		
Irregular/disarrayed dermal epidermal junction[39,44,64]	3		
Nonvisible papillary contours[40,69]	2		
Loss of dermal papillae (flat DEJ)[31]	1		
Poorly visualized dermal papillae[54]	1		
DEJ disarray[57]	1		
Disarrangement at the DEJ[77]	1		
Absence of papillae[77]	1		
Weighted subtotal	**46**		
Terms associated with regular dermal papilla			
Edged papillae[4,6,23,28,36,48-50,52,57,58,63,65,67-72,74,77]	22	Dermal papillae with clearly outlined contours; they may result from single cells forming rims around the papillae ("rings"), or by "junctional nests" constituted by compact melanocytic aggregates with sharp borders	Segura et al, 2009[23] Pigmented basal keratinocytes and melanocytes along the sides of the rete ridges
Rings[64]	1		
Weighted subtotal	**23**		

Continued

Table I. Cont'd

RCM term	Use frequency of RCM term, n	Definition	Part of an algorithm	Histopathologic correlates
Terms describing the presence of "atypical" cells at the DEJ				
Atypical cells at the DEJ[29,33,39,42,48,49,67,70,76,78]	10	Presence of bright round or dendritic nucleated cells that are abnormally large in size (>50 μm), display unusual contour (eg, triangular, star shaped) or have large and eccentric nuclei at the DEJ	Borsari et al, 2018[25]; Guitera et al, 2010[4]	Proliferation of atypical melanocytes as solitary units along the DEJ
Cytologic atypia[25,30,41,53,56,59,60,63,65]	9			
Marked atypia of basal cells[6,23,52,58,72]	5			
Atypical cells[40,68]	2			
More than 3 atypical cells at the junction in 5 images[4]	1			
Marked cell atypia in the basal layer[75]	1			
Bright nucleated cells[26]	1			
Scattered bright structures[31]	1			
Predominance of single cells over nests[32]	1			
Large dendritic or round cells at the epithelial-stromal junction and/or in the stroma[35]	1			
Atypical nucleated cells at the DEJ[36]	1			
Cellular atypia in the DEJ[37]	1			
Atypical cells at basal layer[43]	1			
Mild and marked cellular atypia[4]	1			
Atypical and pleomorphic refractile cells[55]	1			
Bright, highly refractile particles[55]	1			
Presence of large visible cells[68]	1			
Terms describing atypical cells with other shapes at the DEJ				
Spindled cells[49,57,69,†]	3			
Terms describing the presence of "atypical" cells with additional features				
Focal increase of atypical melanocytes and nests[27]	1			
Weighted subtotal	**43**			
Terms describing the presence of round-shaped junctional aggregates, regular				
Junctional nests[5,40,48,49,55-58,67-69,72,74,77,78]	15	Elongated and branching tubular structures with heterogeneous reflectance harboring aggregates and individual polymorphous nucleated cells at the DEJ; they often bulge into dermal papillae		Junctional nested proliferation of melanocytes.; elongated junctional nests of melanocytes may bridge between adjacent rete ridges
Junctional clusters[4,23,58,63,65,68,71,72]	8			
Terms describing the presence of elongated, tubular junctional aggregates				
Junctional thickening[4,26,43,58,63,65,68,69,71,72,74]	11			
Cord-like rete ridges[27]	1			
Nonhomogeneous cellularity[67]	1			
Terms describing the presence of short/bridging tubular junctional aggregates				
Mitochondria-like structures[77]	1			
Short interconnections[67]	1			
Weighted subtotal	**38**			
Terms describing sheet-like proliferation of melanocytes at the DEJ				

Sheet-like structures[5,23,24,43,49,56,67-69,72,74,77]	12	Cells distributed at the transition of the DEJ showing loss of dermal papillae not aggregated in clusters but closely distributed in the same plane with the loss of dermal papillae		Florid lentiginous proliferation of atypical melanocytes along the DEJ; mostly seen in melanomas in sun-damaged skin
Sheet of cells[4,6,30,52,58]	5			
Sheet-like[25]	1			
Sheets of round to dendritic nucleated cells[26]	1			
Tangled filaments/dendrites crossing the papillae[41]	1			
Sheets of mainly dendritic atypical cells[27]	1			
Weighted subtotal	**21**			
Terms describing elongated structures bulging from the hair follicles				
Medusa head-like[24,64]	2	Small protrusions or elongated protrusions from hair follicles; they correspond to the "Medusa head-like" structure when distributed around the entire perimeter of the follicle		N/A
Bulging around hair follicle[64]	1			
Weighted subtotal	**3**			
Superficial dermis (n = 68; 32.8%)				
Terms describing the presence of solitary melanocytes in the papillary dermis				
Nucleated cells within the dermal papillae[4,6,28,29,36,37,52,59,61,68,76]	11	Round to oval or triangular cells with well-demarcated bright cytoplasm and well-demarcated dark nucleus infiltrating dermal papillae	Guitera et al, 2010[4]	Presence of atypical melanocytes in the superficial (papillary) dermis
Nucleated cells in the dermis[58,69,72,75]	4			
Isolated cells in the papilla[72,74]	2			
Dermal infiltration of roundish cells[64]	1			
Atypical melanocytes within the upper dermis[27]	1			
Atypical cells in the dermal papilla[33]	1			
Dermal nucleated cells[57]	1			
Isolated cells within the upper dermis[63]	1			
Isolated cells within the papillary dermis[65]	1			
Atypical nucleated cells in dermis[67]	1			
Atypical nucleated dermal cells[23]	1		Segura et al, 2009[23]	
Atypical cells infiltrating papillary dermis[78]	1			
Spindle cells in superficial dermis[58,‡]	1			
Weighted subtotal	**27**			
Terms describing the presence of cohesive nests of melanocytes in the papillary dermis				
Dense nests[4,25,48,49,56,58,60,67-72,77]	14	Compact aggregates with sharp margins and monomorphous cells in which it is difficult to discern individual cell borders	Borsari et al, 2018[25]	Round to oval junctional or dermal nests of melanocytes
Dermal nest[5,23,40,43,48,55,57,67,78]	9			
Melanocytic cell nests[45-47]	3			
Dense clusters[63,65,74]	3			
Dense regular nests[23,75]	2			
Confluence of nests[69,†]	1			
Dermal cell clusters[72]	1			
Nesting[25]	1			
Weighted subtotal	**34**			
Terms describing the presence of discohesive/irregular nests of melanocytes in the papillary dermis				

Continued

Table I. Cont'd

RCM term	Use frequency of RCM term, n	Definition	Part of an algorithm	Histopathologic correlates
Dense and sparse nests[25,30,48,49,56,60,67,70]	8	Clusters of somewhat loosely aggregated cells in which some of cells have clearly defined cell borders and little dark space can be seen in between some, but not all, cells		Irregular or discohesive nests of melanocytes
Dishomogeneous nest[4,6,52,58,69,72,74]	7			
Sparse nest[58,68,69,72,74]	5			
Nonhomogeneous nests[23,68]	2			
Irregular clods[30]	1			
Atypical nucleated cells arranged in nests[41]	1			
Aggregates of atypical cells[62]	1			
Dishomogeneous clusters[63]	1			
Sparse cell clusters[65]	1			
Marked pleomorphism within nests[49]	1			
Discohesive junctional nests[77]	1			
Dense irregular nests[75]	1			
Dense dishomogeneous clusters[75]	1			
Weighted subtotal	**31**			
Terms describing the presence of "cerebriform" aggregates in the dermis				
Cerebriform nest[5,6,23,30,36,37,40,48,52,53,56,58,68,69,72,74-76]	18			Nodular aggregates of atypical melanocytes in melanoma with dermal component
Cerebriform clusters[49,59,63,65,75]	5			
Weighted subtotal	**23**			
Terms describing the presence of melanophages in the papillary dermis				
Plump cells[23,33,56-58,63,69,70,72-75,77]	13	Irregularly shaped bright cells with ill-defined borders and usually no visible nucleus	Borsari et al, 2018[25]	Melanophages
Melanophages[25,26,30,50,51,60,64,65]	8			
Plump-bright cells[4,40,68]	3			
Bright, round-to-triangular, nonnucleated cells[26]	1			
Weighted subtotal	**25**			
Terms describing the presence of inflammation (other than melanophages) in the papillary dermis				
Inflammation[38,49]	2	Bright spots and small bright particles in the dermis		Inflammatory cells (other than melanophages)
Bright spots[56,69]	2			
Inflammatory infiltrate[48,67]	2			
Dermal inflammation[24]	1			
Dermal bright cells[51]	1			
Bright small cells and/or hyperreflective spots[68]	1			
Small bright cells and particles[72]	1			
Bright particles[73]	1			
Bright hyperreflecting spots[23]	1			
Bright dots[77]	1			
Weighted subtotal	**13**			
Terms describing patterns of collagen in the papillary dermis				

Bundled collagen[72,74,77]	3	Elongated fibrillar structures (1-5 μm) without cellular component distributed side by side through the dermis	Various correlates ranging from normal collagen, to scar-like collagen, to solar elastosis
Reticulated collagen[72,74,77]	3		
Coarse collagen[24,70]	2		
Bright fibrillar structures[75]	1		
Thickened collagen/curled fibers (elastosis)[64]	1		
Stromal fibre (“collagen”) morphology[48]	1		
Highly reflecting fibers[50]	1		
Curled highly refractive collagen fibers[4]	1		
Fibroplasia[67]	1		
Reticulated fibers[68]	1		
Broadened reticulated fibers[68]	1		
Thick cordons[68]	1		
Weighted subtotal	**17**		
Terms describing the presence of prominent blood vessels in the papillary dermis			
Enlarged vessels[23,50,75]	3	Blood vessels appear as dark tubular structures in the dermis in which movement of bright round cells (white blood cells) is seen. Irregular vessels refer to blood vessels with abnormal diameter, density, or orientation compared to normal skin.	Dilated or increased vascularity in the superficial dermis
Tortuous morphology of vessels[33]	1		
Irregular vessels[40]	1		
Prominent vascularity[56]	1		
Horizontal vessels[58]	1		
Atypical vessels[59]	1		
Weighted subtotal	**8**		
Terms with definition not available (n = 9; 4.7%)			
Nests (NOS)[4,24,58,64,69]	5	—	—
Disarray of melanocytic architecture[45-47]	3	—	—
Ill-defined follicle contour[64]	1	Aspect of the external border of the hair follicle, defined according to its outline	—
Atypical cells with dark halo[4,*]	1	—	—
Oval cells[57]	1	—	—
Elongated cells[57]	1	—	—
Triangular cells[57]	1	—	—
Cord-like structures[62]	**1**	Pseudonetwork on dermoscopy	—
DEJ atypia[57]	1		
N/A total	**15**		
Total terms (N = 191; 100%)			

DEJ, Dermoepidermal junction; *N/A,* not available; *NOS,* not otherwise specified; *RCM,* reflectance confocal microscopy.
*Described in amelanotic/hypomelanotic melanoma.
†Described in Spitzoid lesions.
‡Described in desmoplastic melanoma.

Table II. Reflectance confocal microscopy terms used to describe the patterns of melanocytic lesions at low magnification

RCM term	Use frequency of RCM term, n	Definition	Histopathologic correlates
Terms with definition (n = 15)			
Ringed pattern[5,24,25,38-42,48,49,56,62,67,70,71]	15	A pattern consisting of edged-papillae presenting a demarcated rim of bright basal cells forming "rings"	Lentiginous or small-nested junctional proliferation of melanocytes
Weighted subtotal	**15**		
Meshwork pattern[5,24,25,30,38-42,48,56,62,67,70,71,77]	16	Enlarged interpapillary spaces predominantly constituted by junctional thickenings and/or nonedged papillae	Nested junctional proliferation of melanocytes with bridging between adjacent rete ridges
Weighted subtotal	**16**		
Clod pattern[25,39-42,48,56,67,70,71]	10	A low-magnification pattern composed of predominance of dense compact nests/clusters of melanocytes within the superficial dermis	Dermal nested proliferation of melanocytes
Small clods (<150 μm)[70]	1		
Large clods (>150 μm)[70]	1		
Weighted subtotal	**12**		
Mixed pattern[70]	1	Combination of any of the DEJ patterns (ie, ringed, meshwork or clod pattern)	Melanocytic neoplasms with a junctional and dermal components
Weighted subtotal	**1**		
Nonspecific[25,30,39,41,48,56,67]	7	Lack of a recognizable pattern at low-magnification mosaic view of the DEJ (ie, absence of ringed, meshwork, or clod pattern); usually associated with abrupt or vague epidermal-dermal transition	Melanocytic proliferation with a flattened DEJ or marked attenuation of the undulation DEJ pattern
Structureless area[38]	1		
Aspecific pattern[60]	1		
Weighted subtotal	**9**		
Asymmetry[47]	1	The overall distribution of confocal structures in one half of the lesion does not mirror those in the other half	Asymmetry
Architectural disorder[41]	1		
Weighted subtotal	**2**		
Peripheral rim of nests[48]	1	Presence of clusters of cells (nests) detectable along the entire perimeter of the lesion	Presence of junctional or dermal nests of melanocytes at the periphery of the lesion
Peripheral melanocytic nests[62]	1		
Rim of nests at the periphery[69]	1		
Weighted subtotal	**3**		
Sharp border cutoff[69]	1	Clear demarcation between lesional and peripheral skin; seen in Spitz nevus.	Sharp demarcation
Weighted subtotal	**1**		
Terms with definition not available (n = 3; 10.3%)			
Uneven pattern[24]	1		—
Undefined epidermal pattern[43]	1		—
Specific pattern[60]	1		—
Weighted subtotal	**3**		
Total for patterns terms (n = 18)	**62**		

DEJ, Dermoepidermal junction; *RCM,* reflectance confocal microscopy.

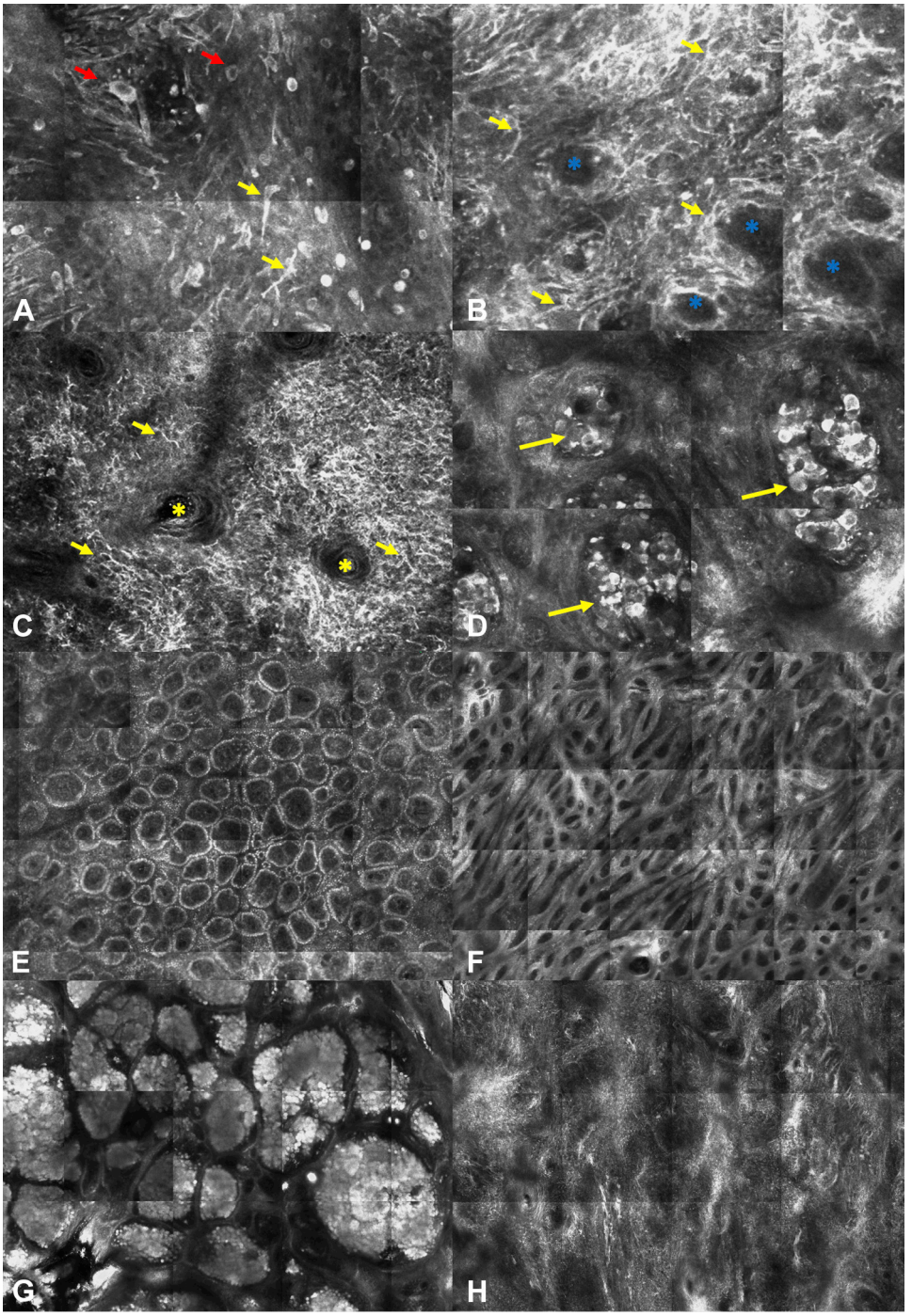


Fig 2. Examples of reflectance confocal microscopy terms. **A-D**, High-magnification/cellular details examples of melanoma features. **A,** Round (red arrows) and dendritic (yellow arrows) pagetoid cells in the epidermis (2.0 × 2.0 mm). **B**, Atypical cells at the dermoepidermal junction (yellow arrows) and nonedged papillae (blue asterisks) (2.0 × 2.0 mm). **C**. Bright, large, dendritic nucleated cells (yellow arrows) with folliculotropism (yellow asterisk shows a hair follicle) in a lentigo maligna melanoma (0.75 × 0.75 mm). **D**, Dishomogeneous (dense and sparse) nest (yellow arrows) at the dermis level (1.0 × 1.0 mm). **E-H**, Low-magnification/patterns examples used to describe melanocytic lesions. **E**, Ringed pattern (2.0 × 1.0 mm). **F**, Meshwork pattern (2.7 × 2.0 mm). **G**, Clod pattern (2.5 × 3.5 mm). **H**, Nonspecific pattern.

Table III. Breakdown of reflectance confocal microscopy terms for melanocytic neoplasms into basic terminology units

Cells/structures	Morphology modifiers/descriptors	Anatomic location/distribution
Relates to melanocytes as individual cells		
Atypical cells	Dendritic	Pagetoid spread
Atypical melanocytes	Enlarged	Pagetoid pattern
Bright nucleated cells	Hyporeflective/dark	Pagetoid infiltration
Cell atypia	Irregularly bright	Widespread
Cells (NOS*)	Large	Focal
Cellular atypia	Pleomorphic	Folliculotropism
Cytological atypia	Round	Infiltrating adnexal structures
Melanocytic cells	Spindled	Nonspecified
Melanocytes	With halo	In the dermal papillae
Nucleated cells		At the DEJ
Pagetoid cells		Dermal infiltration
		Infiltrating papillary dermis
		At the periphery
Relates to dendritic processes without visible cell body		
Branching dendrites†	Composite dendrites	
Dendritic processes†	Simple dendrites	
Tangled lines†	Coarse dendrites	
Relates to aggregated melanocytes		
Aggregates of atypical cells	Cerebriform	Around the hair follicle
Bulging	Dense	Junctional
Cells clusters	Dense and sparse	Dermal
Clods	Dense dishomogeneous	
Clusters	Dense irregular	
Junctional thickening	Discohesive	
Medusa head-like	Dishomogeneous	
Melanocytic cell nests	Irregular	
Mitochondria-like structures	Marked pleomorphism (within nest)	
Nesting	Nonhomogeneous	
Nests	Pleomorphism (within nest)	
Sheet-like	Sparse	
Related to keratinocytes		
Acanthosis	Atypical	
Basal cells	Broadened (honeycomb)	
Cobblestone pattern	Irregular	
Epidermal disarray	Monomorphic	
Epidermal pattern	Poorly defined	
Honeycomb pattern	Readily detected	
Keratinocyte cell borders	Regular	
Refractile cells	Typical	
Relates to DEJ structures/shape		
DEJ disarray	Absent	
Dermal papillae	Edged	
Papillae	Loss of (papilla/papillary contour)	
Papillary contours	Nonedged	
	Nonvisible	
	Poorly visualized	
	Ringed	
Relates to stromal structures: Inflammatory cells		
Bright dots	Round-to-triangular	Dermal
Bright nonnucleated cells		
Bright particles		
Bright small cells		
Bright spots		

Continued

Table III. Cont'd

Cells/structures	Morphology modifiers/descriptors	Anatomic location/distribution
Dermal bright cells		
Inflammatory infiltrate		
Inflammation		
Melanophages		
Plump cells		
Relates to stromal structures: Stromal fibers		
Bright fibrillar structures	Broadened	
Collagen	Bundled	
Curled fibers	Coarse	
Fibroplasia	Reticulated	
Highly reflecting fibers	Thickened	
Stromal fibre		
Thick cordons		
Relates to stromal structures: Blood vessels		
Vascularity	Atypical	
Vessels	Enlarged	
	Horizontal	
	Irregular	
	Prominent	
	Tortuous morphology	

DEJ, Dermoepidermal junction; *NOS,* not otherwise specified.
"Grainy image" and "epidermal granularity" are not included in the table.
*NOS: the context of the original term implies that "cells" refers to melanocytes.
†*Dendritic structures* is a descriptive term that can pertain to dendritic processes emanating from either melanocytes or from Langerhans cells.

themes, namely, basic terminology units describing melanocytes as individual cells, dendritic processes without visible cell body, aggregated melanocytes, keratinocytes, DEJ structures, inflammatory cells, collagen structures, and blood vessels (Table III).

Low-magnification/architectural patterns terms

By categorizing low-magnification terms into likely synonymous clusters, we reduced 18 individual terms to 8 likely synonymous group terms (55.5% reduction) (Table II). Three additional terms (16.6%) lacked a clear definition. When stratifying by anatomic level, all terms were ascribed to the DEJ and/or superficial dermis level and none to the epidermis.

DISCUSSION

In the present systematic review, describing the RCM terminology of melanocytic lesions, we extracted 209 terms from 59 studies. We grouped the individual RCM terms into likely synonymous clusters based on similarity in definition and/or histopathology correlates, and we excluded terms lacking a clear definition, potentially distilling 40 nonredundant terms from the 209 initial terms (80.8% reduction).

In a systematic review of RCM terminology for describing NMLs, we found that the average number of uses per term was only 1.6 times. Here, we found that RCM terms from melanocytic neoplasms were used with an average frequency of 3.1. A higher average use frequency for melanocytic neoplasms, compared to NMLs, might be attributed to the previous consensus on melanocytic terminology in 2007.[18] We also found in the present study a higher average use frequency for low-magnification terms compared to high-magnification terms (average use of 3.4 vs 3.0, respectively). This may suggest higher consistency in the use of low-magnification RCM terms for melanocytic lesions.

We also found that RCM melanocytic terms are often composite (71.4%). This complexity may emanate from the fact that multiple RCM attributes need to be weighed to differentiate melanoma from challenging nevi—such as the shape, size, and anatomic distribution of individual or aggregated melanocytes. Toward simplifying RCM terminology, we extracted 125 basic terminology units from the 191 high-magnification RCM terms and categorized them into individual units describing "cells" or "structures," followed by the morphologic attributes of these cells/structures and their anatomic distribution. This is akin to extracting basic words from complex sentences. This lays the groundwork for an

expert agreement study that will eliminate redundancy and identify from the list the best basic descriptors (words) and composite criteria (sentences).

Creating a concise list of pertinent RCM terms for the diagnosis of melanocytic lesions is an important step toward widespread adaptation of RCM. Along similar lines, Pellacani et al[21] recently published an expert consensus study in which the experts identified 18 principal RCM terms for diagnosis of melanocytic and nonmelanocytic lesions. These terms were then further clustered into 2 melanoma-specific key features (atypical cells [at any level] and DEJ disarray), 1 basal cell carcinoma–specific key feature (basaloid cords/islands), and 1 squamous cell carcinoma–specific key feature (keratinocyte disarray). Identification of 1 of these 4 key features by novices was associated with a skin cancer diagnostic sensitivity of 91% and specificity of 57%.[21] This study highlighted that a simplified short list of skin cancer key criteria could be easily learned and successfully used by novice RCM readers. A similar approach for triaging lesions has been proposed by simplified dermoscopy algorithms.[79] However, the RCM diagnosis of challenging melanocytic cases by experts requires a more elaborate set of criteria.

Limitations

We included only full-text articles in English to allow direct comparisons of terms without translation bias. RCM terms published in non-English papers may have been missed. Non–peer-reviewed articles (eg, book chapters) were excluded, and some terms used by the experts could have been missed. The weightage attributed to RCM terms may be influenced by the frequency of publication for individual researchers or research groups. Also, some terms were grouped together, but further studies are needed to determine if more granularity is relevant or needed (eg, collagen and elastosis). Finally, the literature search was conducted in August 2018; therefore, some recent key terms might have been overlooked.

CONCLUSION

We propose a more concise glossary of RCM terms for the diagnosis of melanocytic lesions. By grouping the RCM terms based on likely synonymous definitions and by eliminating terms lacking a clear definition, the list could be reduced by more than 80%. This systematic review lays the groundwork for an expert Delphi consensus for melanocytic lesions terminology. Furthermore, a concise glossary of RCM terms can facilitate standardizing of RCM diagnosis reports, teaching of novices, and communicating of research findings.

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