DOI: 10.1111/jdv.17059 JEADV

ORIGINAL ARTICLE

Dermatoscopy of combined blue nevi: a multicentre study of the International Dermoscopy Society

J. Stojkovic-Filipovic,[1,*] D. Tiodorovic,[2] A. Lallas,[3] B.N. Akay,[4] C. Longo,[5,6] C. Rosendahl,[7] D. Dobrosavljevic,[1] G. Nazzaro,[8] G. Argenziano,[9] I. Zalaudek,[10] I. Tromme,[11] P. Tschandl,[12] S. Puig,[13,14] S. Lanssens,[15] H. Kittler[12]

[1]Clinic of Dermatology and Venereology, Clinical Center of Serbia, Department of Dermatology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[2]Clinic of Dermatovenereology, Clinical Center of Nis, Medical Faculty, University of Nis, Nis, Serbia
[3]First Department of Dermatology, Aristotle University, Thessaloniki, Greece
[4]Medicine Faculty, Department of Dermatology, Ankara University, Ankara, Turkey
[5]Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy
[6]Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia, Centro Oncologico ad Alta Tecnologia Diagnostica-Dermatologia, Reggio Emilia, Italy
[7]Faculty of Medicine, The University of Queensland, Capalaba, QLD, Australia
[8]Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[9]Dermatology Unit, University of Campania, Naples, Italy
[10]Department of Dermatology, University of Trieste, Trieste, Italy
[11]Dermatology Department, King Albert II Institute, Cliniques Universitaires St Luc, Brussels, Belgium
[12]Department of Dermatology, Division of General Dermatology, Medical University of Vienna, Vienna, Austria
[13]Dermatology Department, Melanoma Unit, Hospital Clínic de Barcelona, IDIBAPS, Universitat de Barcelona, Barcelona, Spain
[14]Centro de Investigación Biomédica en Red de Enfermedades Raras, Instituto de Salud Carlos III, Barcelona, Spain
[15]Dermatologie Maldegem, Maldegem, Belgium
*Correspondence: J. Stojkovic-Filipovic. E-mail: sf.jelena@gmail.com

Abstract

Background Combined blue nevi (CBN) may mimic melanoma and are relatively often biopsied for diagnostic reasons.

Objective To better characterize CBN and to compare it with melanoma.

Methods We collected clinical and dermatoscopic images of 111 histologically confirmed CBN and contrasted their dermatoscopic characteristics with 132 partly blue coloured melanomas. Furthermore, we compared the accuracy of human experts using pattern analysis with a computer algorithm based on deep learning.

Results Combined blue nevi are usually flat or slightly elevated and, in comparison with melanoma, more frequent on the head and neck. Dermatoscopically, they are typified by a blue structureless part in combination with either brown clods (n = 52, 46.8%), lines (n = 28, 25.2%) or skin-coloured or brown structureless areas (n = 31, 27.9%). In contrast with melanoma, the blue part of CBN is more often well defined (18.9% vs. 4.5%, $P < 0.001$) and more often located in the centre (22.5% vs. 5.3%, $P < 0.001$). Melanomas are more often chaotic (OR: 28.7, 95% CI: 14.8–55.7, $P < 0.001$), have at least one melanoma clue (OR: 10.8, 95% CI: 5.2–22.2 $P < 0.001$) in particular white lines (OR: 37.1, 95% CI: 13.4–102.9, $P < 0.001$). Using simplified pattern analysis (chaos and clues), two raters reached sensitivities of 93.9% (95% CI: 88.4–97.3%) and 92.4% (95% CI: 86.5–96.3%) at corresponding specificities of 59.5% (95% CI: 49.7–68.7%) and 65.8% (95% CI: 56.2–74.5%). The human accuracy with pattern analysis was on par with a state-of-the-art computer algorithm based on deep learning that achieved an area under the curve of (0.92, 95% CI: 0.87–0.96) and a specificity of 85.3% (95% CI: 76.5–91.7%) at a given sensitivity of 83.6% (95% CI: 72.5–91.5%).

Conclusion CBN usually lack melanoma clues, in particular white lines. The accuracy of pattern analysis for combined nevi is acceptable, and histopathologic confirmation may not be necessary in exemplary cases.

Received: 30 August 2020; Accepted: 13 November 2020

Conflict of interest

The manuscript has been seen and approved by all authors, and their statements are listed below: Dr. J. Stojkovic-Filipovic, Dr. Tiodorovic, Dr. Lallas, Dr. Akay, Dr. Longo, Dr. Rosendahl, Dr. Dobrosavljevic, Dr. Nazzaro, Dr. Argenziano, Dr. Zalaudek, Dr. Tromme and Dr. Lanssens have nothing to disclose. Dr. Tschandl reports personal fees from Silverchair and grants from MetaOptima Technology, outside the submitted work. Dr. Puig reports grants and personal fees from

AMGEN; non-financial support from AVENE; personal fees from BMS; personal fees from CANTABRIA; grants, personal fees and non-financial support from ISDIN; grants, personal fees and non-financial support from La Roche Posay; grants, personal fees and other from Roche; grants, personal fees and other from Sanofi; grants and personal fees from Sun-farma; non-financial support from Abbvie; grants from Novartis; personal fees and other from Pfizer; personal fees and other from Regeneron; grants, personal fees, non-financial support and other from Almirall; and other from MSD, outside the submitted work. Dr. Kittler reports personal fees and other from Fotofinder; other from Heine; other from Derma Medical Systems; other from 3Gen, outside the submitted work, and received fees for lectures from Novartis, Allmiral and Pelpharma; and an educational grant from Eli Lilly.

Funding sources

None reported.

Introduction

There is no universal, comprehensive and consistent definition of combined nevi (CN). From a histopathologic point of view, CN are characterized by the presence of two or more cytologically distinct populations of melanocytes in the same naevus.[1,2] This definition is based on cytomorphology, which is not discernible *in vivo*, neither by examination with the unaided eye nor by dermatoscopy. Among the many possible combinations, those most frequently encountered in practice are superficial congenital naevus combined with blue naevus, Spitz naevus combined with Clark naevus ('SPARK'), superficial congenital nevi combined with deep penetrating naevus, and blue naevus combined with Spitz naevus ('BLITZ'). CN that contain portions of a blue naevus [combined blue nevi (CBN)] are distinct, because they are typified by a blue structureless part that is easily recognizable with the unaided eye or by dermatoscopy. Because other types of CN are not discernable *in vivo*, the term 'combined naevus' when used by clinicians usually refers to the 'combined blue naevus' subtype.

From a dermatoscopic point of view, CBN are alarming because they may mimic melanoma. They may be asymmetric with regard to pattern or colour ('chaotic'), and the blue colour is not only a hallmark of CBN, but also an important clue to melanoma. Because of the distinctive clinical appearance and because it is a melanoma mimic, CBN are relatively often biopsied and are, according to our experience, more frequent than other subtypes of CN. The current literature of the dermatoscopy of CBN is limited to case reports or small case series.[3–9] Schweizer *et al.*[10] recently published the largest cases series including 36 CBN from various centres.

The aims of this study were to better characterize the dermatoscopy of CBN on a larger series of cases and to compare their dermatoscopic characteristics with melanomas that are partly blue in colour.

Material and methods

After internal review by the study committee of the International Dermoscopy Society (IDS), the IDS officially announced the study on their web portal. The call was open from December 2016 to May 2018. The study protocol was approved by the ethics review board of the Clinical Centre of Serbia, Belgrade, Serbia No57/2. The study coordinator (JSF) asked members of the IDS for high-resolution close-up and dermatoscopic images of consecutive cases of CBN and corresponding meta-data such as age, gender and anatomic site. Exclusion criteria were lack of histopathologic confirmation, out-of-focus images or cases in which only parts of the lesion were photographed without the possibility to inspect the entire lesion. The study coordinator received 186 cases from eight different countries (Austria, Australia, Belgium, Greece, Italy, Serbia, Spain and Turkey), of which 125 fulfilled the inclusion criteria. Fourteen cases were excluded because they were duplicates of already submitted cases, leaving 111 CBN for further analysis. To compare the dermatoscopic characteristics of CBN with similar looking melanomas, two authors (JSF, HK) manually searched the image archive of the International Skin Imaging Collaboration (ISIC) for dermatoscopic images of melanomas that are partly blue in colour. Of 2270 images of melanoma reviewed, 132 contained blue parts and were included in the analysis.

Assessment of close-up and dermatoscopic images

We used the close-up images to determine whether a lesion is flat or slightly raised ('flat'), or significantly raised ('raised'). An experienced reader (HK) described the dermatoscopy of CN according to revised pattern analysis and the terminology suggested by the 3rd consensus conference of the IDS.[11] Two other readers (JFS and TD) independently rated the presence or absence of chaos and melanoma clues in all CBN and melanomas according to the chaos and clues algorithm,[12] on a computer screen using a predefined questionnaire. Since a blue structureless area is present in CN per definition, this feature was not counted as a melanoma clue for the purpose of this study. Readers were not blinded with regard to the diagnosis.

Convolutional neural network

As previously described,[13] we fine-tuned a single convolutional neural network for classification of seven different categories including nevi and melanoma, as included in the HAM10000 dataset.[14] Training was performed on NVIDIA graphics processing

Table 1 General characteristics of combined blue nevi and control melanomas

	Combined blue nevi (n = 111)	Melanoma (n = 132)	P-value
Age (years), median (25th–75th quartile)	37 (21.5–49)	65 (50–75)†	<0.001
Female sex	44 (39.6%)	42(39.3%)	0.38
Anatomic site			0.01
Head and neck	23 (20.7%)	12 (9.8%)	
Trunk	54 (48.6%)	51 (41.5%)	
Upper extremities	18 (16.2%)	26 (21.1%)	
Lower extremities	16 (14.4%)	34 (27.6%)	
Clinical appearance			
Flat	69 (62.2%)	60 (45.5%)	0.01
Raised	42 (48.8%)	72 (54.5%)	
Appearance of blue part			
Proportion of lesion covered (%), mean (SD)	14.7 (9.4)	13.7 (10.2)	0.30
Circumscription			
Well defined	21 (18.9%)	6 (4.5%)	<0.001
Ill defined	90 (81.1%)	126 (95.5%)	
Distribution			
Central	25 (22.5%)	7 (5.3%)	<0.001
Eccentric	86 (77.5%)	125 (94.7%)	
Peripheral expansion			
Touches the edge	37 (33.3%)	54 (40.9%)	0.23
Does not touch the edge	74 (66.7%)	78 (59.1%)	

†Age was missing in six melanoma cases.

units (GPUs) using the PyTorch framework and a ResNet34 architecture, with weights initiated by pretraining on ImageNet data. Class-weighted cross-entropy served as the loss function. The network theoretically provides probabilities for seven different disease categories, but for the differentiation of CBN vs. melanoma we used only the outputs of the two groups 'melanoma' and 'naevus'.

Statistical analysis

We report descriptive statistics for the readings of both raters. We found no statistically significant differences between the readings of raters (data not shown). Continuous data are given as mean and the standard deviation, or as median and interquartile range. We used t-tests or Mann–Whitney U-tests to compare continuous variables and combined the readings of both raters to calculate common odds ratios and their respective 95% confidence interval with the Cochran–Mantel–Haenszel statistics (CMH). We used the Woolf's test to test for homogeneity of odds ratios and the Bonferroni correction for *post hoc* analysis of individual raters. A P-value < 0.05 was considered statistically significant. Calculations and plotting were performed using R version 3.4.0 (R-3.4.0 for Windows (32/64 bit)).

Results

General characteristics of CBN and comparison with melanomas

Of 111 patients with CBN, 67 (60.4%) were males and 44 (39.6%) females. The median age was 37 years (25th–75th percentile: 22–49 years). Patients with melanomas were significantly older (median age: 65 years, 25th–75th percentile: 50–75 years, $P < 0.001$). With regard to anatomic site, most CBN (n = 54, 48.6 %) and most melanomas (n = 51, 41.5%) were located on the trunk. In comparison with melanoma, CBN were more often located in the head and neck region (n = 23, 20.7% vs. n = 12, 9.8%) and less often on the lower extremities (n = 16, 14.4% vs. n = 34, 27.6%, Table 1). Most CBN were flat or slightly elevated (n = 69, 62.2%). Dermatoscopically, CBN are typified by a blue structureless part in combination with either brown clods (n = 52, 46.8%), lines (n = 28, 25.2%), or skin-coloured or brown structureless areas (n = 31, 27.9%). In contrast with melanoma, the blue part of CBN is more often well defined (18.9%% vs. 4.5%, $P < 0.001$) and more often located in the centre (22.5% vs. 5.3%, $P < 0.001$).

Pattern analysis of CBN and melanomas

Two raters independently scored CBN and melanomas according to simplified pattern analysis (chaos and clues).[12] In contrast with CBN, melanomas were more often chaotic (common OR: 28.7, 95% CI: 14.8–55.7, $P < 0.001$) and were more likely to have at least one melanoma clue (common OR: 10.8, 95% CI: 5.2–22.2 $P < 0.001$). A blue structureless area, which was present in all CN per definition, was not counted as a melanoma clue. We found the highest odds ratio of a single melanoma clue for white lines (common OR: 37.1, 95% CI: 13.4–102.9, $P < 0.001$). The frequencies of all melanoma clues by diagnosis and by rater are given in Table 2.

Table 2 Evaluation according to pattern analysis (chaos and clues)

	Observer 1		Observer 2		Common odds ratio (95% CI)	*P*-value
	CBN (*n* = 111)	Melanoma (*n* = 132)	CBN (*n* = 111)	Melanoma (*n* = 132)		
Chaos	46	125	54	128	28.7 (14.8–55.7)	<0.001
White lines	2	57	2	50	37.1 (13.4–102.9)	<0.001
Pseudopods (radial lines)	4	39	4	36	12.2 (5.5–27.2)	<0.001
Thick reticular lines	5	37	5	37	8.3 (4.1–16.4)	<0.001
Grey structures†	67	100	74	96	1.65 (1.12–1.44)	0.01
Eccentric structureless area	88	122	88	118	28.6 (14.8–55.7)	<0.001
Polymorphous vessels	8	47	7	48	7.8 (4.3–13.9)	<0.001
Polygons	0	4	0	5	NA	NA
Black or brown dots	23	34	26	49	1.6 (1.1–2.4)	0.03
Ulceration	3	19	3	18	5.9 (2.4–14.2)	<0.001

CBN, combined blue nevi.
†Since blue structures are present in combined blue nevi per definition, the colour blue was not counted as a melanoma clue for the purpose of this study.

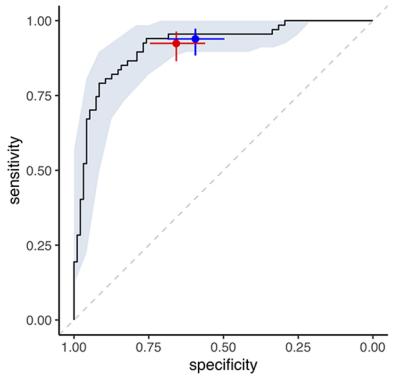

Figure 1 Diagnostic accuracies of two human raters compared to the AUC curve of the convolutional neural network.

Diagnostic accuracy

Using the chaos and clues algorithm, the two raters reached sensitivities of 93.9% (95% CI: 88.4–97.3%) and 92.4% (95% CI: 86.5–96.3%) at corresponding specificities of 59.5% (95% CI: 49.7–68.7%) and 65.8% (95% CI: 56.2–74.5%). A state-of-the-art computer algorithm based on deep learning achieved an area under the curve of 0.92 (95% CI: 0.87–0.96). Assuming that a probability of >0.5 denotes melanoma, the algorithm reached a sensitivity of 83.6% (95% CI: 72.5–91.5%) and a specificity of 85.3% (95% CI: 76.5–91.7%) The diagnostic accuracies of the two human raters fell close to the ROC curve of the algorithm and were within the 95% confidence intervals of the curve as highlighted in Fig 1.

Discussion

Although CN are rare, CBN, the most frequent variant of CN, are often removed for diagnostic reasons because they share dermatoscopic criteria with melanoma. The blue structureless zone of CN may resemble the 'blue veil' of melanoma and, like melanomas, CBN are often asymmetric with regard to colour and pattern. Although dermatoscopy improves the diagnosis of pigmented lesions in comparison with inspection with the unaided eye in general, it is uncertain if it provides sufficient accuracy to differentiate between melanoma and CBN in practice. Here, we describe the clinical and dermatoscopic characteristics of CBN and show that they differ significantly from melanoma. In particular, we demonstrate that sufficiently trained physicians can reliably differentiate between CBN and melanoma using dermatoscopy.

We demonstrate that CBN are flat or slightly elevated lesions that are most often located on the trunk or on the head and neck. The reason for the site specificity of CBN is unknown, but it is in line with the observation that blue nevi are relatively common on the scalp in comparison with other body sites. It is not surprising that individuals with CBN were significantly younger than patients with melanoma, because CBN are considered congenital, although they are usually not visible at birth,[15] and the risk of melanoma increases with age. This set of information could be useful for clinicians to estimate the pretest probability of CBN or melanoma before using dermatoscopy. The pretest probability for CBN will be higher in flat blue lesions of young patients on the head and neck area, and lower for elevated blue lesions in old patients on the leg.

Because it is required criterion per definition, all CBN have blue structureless area on dermatoscopy. From a histopathologic point of view, the blue structureless area corresponds the blue naevus component of the CBN, which is typified by strands of spindle shaped melanocytes in the dermis that are replete of melanin and accompanied by melanophages.[15] Here, we demonstrate that this structureless blue area of CBN is typically well defined and often, albeit not always, located in the centre of the

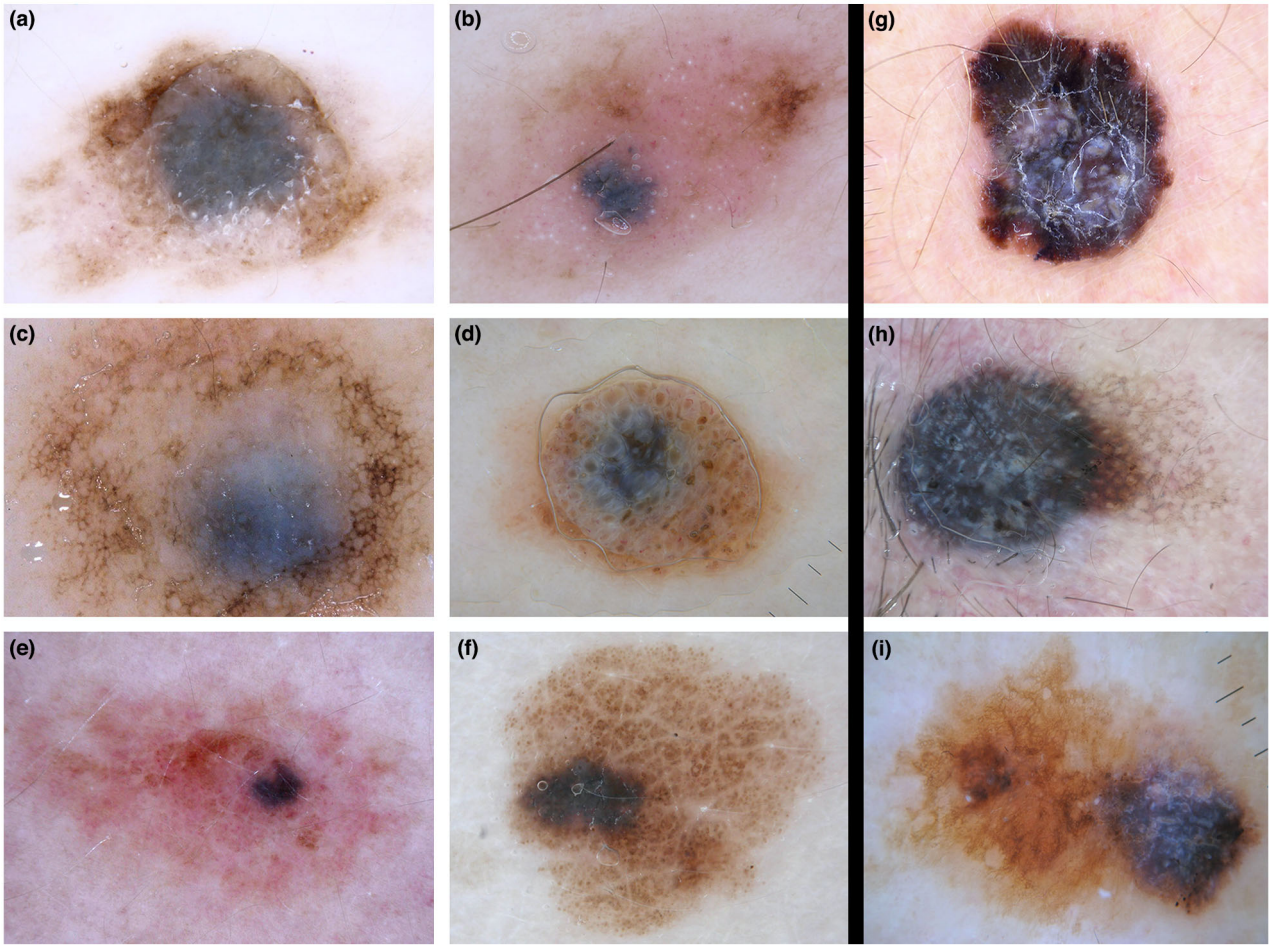

Figure 2 Typical examples of combined blue nevi (CBN) and melanomas with blue parts. (a) CBN with well-defined blue structureless area in the centre, structureless brown and brown clods at the periphery, no melanoma clues; (b) CBN with well-defined blue structureless area and reticular lines at the periphery, no melanoma clues; (c) CBN with eccentric structureless blue, reticular lines at the periphery, no melanoma clues; (d) CBN with eccentric structureless blue and brown clods at the periphery; (e) CBN with eccentric and well-defined structureless blue and structureless brown; (f) CBN with eccentric structureless blue and brown clods; (g) melanoma with eccentric, ill-defined structureless blue, segmental radial lines (pseudopods), white lines; (h) melanoma with eccentric, rather well-defined structureless blue, grey dots, grey circles, segmental radial lines, white lines; (i) melanoma with eccentric and ill-defined structureless blue, thick reticular lines, grey dots, and white lines.

lesion. In these typical cases, the overall presentation of the CBN will be symmetrical with regard to colour and structure and not chaotic.[10,16] This presentation is also known as the targetoid combined blue naevus type.[16] A pattern of brown clods accompanied the blue structureless pattern in most cases of CBN. Less frequently, we observed the reticular pattern in addition to blue structureless.

A significant proportion of CBN in our series showed an asymmetric combination of colours or patterns (chaos). If chaotic, however, most CBN lack melanoma clues such grey structures, pseudopods/radial lines, thick reticular lines, ulcerations, polygons and, in particular, white lines. In contrast, the 'blue veil' of melanoma is typified by shiny white lines when viewed in polarized mode, Fig. 1. Because we had incomplete information on whether dermatoscopy images were taken in polarized or non-polarized mode, we could not further analyse this potentially confounding factor. Our observations are in line with smaller case series[3,6,16,17] and with the results of a recent study by Schweizer *et al.*,[10] in which the authors reported a relatively low frequency of melanoma clues in CBN.

We also tested the accuracy of the 'chaos and clues' algorithm, a simplified version of pattern analysis,[12] for the differentiation

of CBN from melanomas with a blue part. In our study, using the chaos and clues algorithm, the two experienced raters reached sensitivities of 93.9% and 92.4% at corresponding specificities of 59.5% and 65.8%. Motivated by the encouraging results of the study of Fink *et al.*[18] and by the recent advances in machine learning for the diagnosis of skin cancer,[19] we used a convolutional neural network to compare the results of humans with a benchmark computer algorithm. The CNN reached a relatively high area under the curve of 0.92, and a sensitivity and specificity of 83.6% and 85.3% at a symmetrical cut-off of 0.5. As shown in Fig. 2, the accuracies achieved by the human raters with the chaos and clues algorithm were in the range of the ROC curve of the CNN.

In summary, we show that CBN can be reliably distinguished from melanoma with blue parts by dermatoscopy and that histopathologic confirmation may not be necessary in exemplary cases. The limitations of this study, such as its retrospective design and that the ratings were performed on a computer screen and not on patients, restrict the conclusions that can be drawn from our data. Since blue parts in melanomas usually indicate a thick and potentially dangerous primary tumour, any skin lesion that shows dermatoscopic blue should be met with caution and the threshold for excision or biopsy should be low.

Acknowledgements

We thank the ISIC Archive (https://www.isic-archive.com) for the melanoma images, which are made available to users under Creative Commons (https://creativecommons.org) licence CC0. Dermatoscopic images used in the figures do not contain individually identifiable health information or have been de-identified in accordance with the requirements in the applicable jurisdiction. For any images that contain personally identifying information, written consent was obtained from the subject.

References

1 Baran JL, Duncan LM. Combined melanocytic nevi: histologic variants and melanoma mimics. *Am J Surg Pathol* 2011; **35**: 1540–1548.
2 Massi G, Leboit PE. Combined nevus. In Histological Diagnosis of Nevi and Melanoma. Steinkopff, Heidelberg, 2004:277–288.
3 de Giorgi V, Massi D, Salvini C *et al*. Dermoscopic features of combined melanocytic nevi. *J Cutan Pathol* 2004; **31**: 600–604.
4 Dermoscopy of melanocytic neoplasms combined blue nevi. *Arch Dermatol* 2004; **140**: 902.
5 Argenziano G. Dermoscopy of melanocytic neoplasms: Targetoid combined blue nevi. *Arch Dermatol* 2004; **140**: 1576.
6 Ferrari A, Lozzi GP, Fargnoli MC, Peris K. Dermoscopic evolution of a congenital combined nevus in childhood. *Dermatol Surg* 2005; **31**(11 Pt 1): 1448–1450.
7 Piccolo D, Altamura D, Lozzi GP, Peris K. Blue-whitish veil-like structure as the primary dermoscopic feature of combined nevus. *Dermatol Surg* 2006; **32**: 1176–1178.
8 Panasiti V, Devirgiliis V, Borroni RG *et al*. Dermoscopy of a plantar combined blue nevus: a simulator of melanoma. *Dermatology* 2007; **214**: 174–176.
9 Yaginuma A, Nobeyama Y, Miyake-Nakano S *et al*. Case of combined nevus showing a speckled distribution pattern. *J Dermatol* 2018; **45**: e232–e233.
10 Schweizer A, Fink C, Bertlich I *et al*. Differentiation of combined nevi and melanomas: case-control study with comparative analysis of dermoscopic features. *J Dtsch Dermatol Ges* 2020; **18**: 111–118.
11 Kittler H, Marghoob AA, Argenziano G *et al*. Standardization of terminology in dermoscopy/dermatoscopy: Results of the third consensus conference of the International Society of Dermoscopy. *J Am Acad Dermatol* 2016; **74**: 1093–1106.
12 Rosendahl C, Cameron A, McColl I, Wilkinson D. Dermatoscopy in routine practice - 'chaos and clues'. *Aust Fam Physician* 2012; **41**: 482–487.
Tschandl P, Rinner C, Apalla Z *et al*. Human-computer collaboration for skin cancer recognition. *Nat Med* 2020; **26**: 1229–1234.
14 Tschandl P, Rosendahl C, Kittler H. The HAM10000 dataset, a large collection of multi-source dermatoscopic images of common pigmented skin lesions. *Sci Data* 2018; **5**: 180161.
15 Kittler H, editor. Dermatoscopy. Pattern Analysis of Pigmented and Non-pigmented Lesions, 2nd edn, Facultas Universitatsverlag, Vienna, 2016.
16 Cabo H. Combined nevi. In Soyer HP, Argenziano G, Hofmann-Wellenhof R, Johr RH, eds. Color Atlas of Melanocytic Lesions of the Skin, Springer, 2007: 97–101.
17 Zalaudek I, Manzo M, Savarese I *et al*. The morphologic universe of melanocytic nevi. *Semin Cutan Med Surg* 2009; **28**: 149–156.
18 Fink C, Blum A, Buhl T *et al*. Diagnostic performance of a deep learning convolutional neural network in the differentiation of combined naevi and melanomas. *J Eur Acad Dermatol Venereol* 2020; **34**: 1355–1361.
19 Tschandl P, Codella N, Akay BN *et al*. Comparison of the accuracy of human readers versus machine-learning algorithms for pigmented skin lesion classification: an open, web-based, international, diagnostic study. *Lancet Oncol* 2019; **20**: 938–947.