Objective: To better characterize the dermoscopic patterns of mucosal lesions in relation to the histopathologic characteristics.

Design: Retrospective and observational study.

Setting: Fourteen referral pigmented lesion clinics in 10 countries.

Patients: A total of 140 pigmented mucosal lesions (126 benign lesions, 11 melanomas, 2 Bowen disease lesions, and 1 metastasis) from 92 females (66%) and 48 males (34%) were collected from October 2007 through November 2008.

Main Outcome Measures: Scoring the dermoscopic patterns (dots, globules, or clods, circles, lines, or structureless) and colors (brown, black, blue, gray, red, purple, and white) and correlation with the histopathologic characteristics.

Results: Based on univariate analysis and 2 diagnostic models, the presence of structureless zones inside the lesions with blue, gray, or white color (the first model) had a 100% sensitivity for melanoma and 92.9% sensitivity for any malignant lesion, and 82.2% and 83.3% specificity for benign lesions in the group with melanoma lesions and the group with malignant lesions, respectively. Based on the colors (blue, gray, or white) only (the second model), the sensitivity for the group with melanoma was 100% and for the group with any malignant lesion was 92.9%, and the specificity was 64.3% and 65.1%, respectively. Patients with malignant lesions were significantly older than patients with benign lesions (mean [SD] ages, 60.1 [22.8] years vs 43.2 [17.3] years, respectively).

Conclusion: The combination of blue, gray, or white color with structureless zones are the strongest indicators when differentiating between benign and malignant mucosal lesions in dermoscopy.

Lesions were collected from October 2007 through November 2008 via an e-mail request sent to all members of the IDS.15 For each lesion, a patient documentation form and clinical and digital dermoscopic polarized and nonpolarized, high-resolution (200-2230 KB), high-quality images in JPEG format were required. The following data were collected for each lesion: (1) sex, (2) age, (3) skin type, (4) smoking history, (5) diagnosis, (6) histopathologic diagnosis, including Breslow tumor thickness for melanoma, and (7) anatomic site of the mucosal lesion. The anatomic sites of the mucosal lesions were divided into lip, labia, glans, prepuce, and other anogenital areas. The latter group included lesions of the perineum and perianal lesions. Exclusion criteria were nonmucosal, tongue, uncertain diagnoses, and nonpigmented tumors.

All included patients provided written or oral informed consent. The approval was waived by the ethics committee. All data and digital images of the mucosal lesions were numbered, anonymized, and sent via e-mail to the study coordinator (A.B.).

Entirely or only partially documented photographed lesions were included. Sufficient quality of the dermoscopic images was requested for reliable recognition of differential structures and colors. According to the standard criteria, the histopathological diagnoses were made by each participating institution. Logistical problems prevented the implementation of a consensus histopathologic evaluation of the collected cases; however, all diagnoses were made by board-certified dermatopathologists with many years of experience. To avoid confusion, the generic terms lentigo, genital lentigo, or labial lentigo were summarized under the term melanotic macule, which is defined as basal hyperpigmentation of the epithelium without clinically significant hyperplasia of melanocytes.

### ANALYSIS OF DERMOSCOPIC IMAGES

All digital images were reviewed in consensus by 3 of us (A.B., H.K., O.S.) blinded from the original histologic diagnosis. Each lesion was scored for the following dermoscopic patterns: (1) a pattern of dots, (2) globules or clods, (3) circles, and (4) lines. If the pattern consisted of pigmented lines, we differentiated between reticular, parallel, and curved lines. If none of the basic elements were present (no dots, globules or clods, circles, or lines) the pattern was termed structureless. We also determined the number of patterns that were present within a single lesion. It is important to note that a single dot or a single line does not constitute a pattern. The term pattern used in this study was defined as a collection of multiple elements of the same type, for example, multiple dots that cover a considerable part of the lesion. With regard to color, we scored the presence of brown, black, blue, gray, red, purple, and white and counted the number of colors present in a lesion.10,11

### STATISTICAL ANALYSIS

Continuous data are given as means (SDs) unless otherwise specified. χ² Tests or Fisher exact tests were used for the comparison of proportions. The Bonferroni correction was used to adjust for multiple comparisons. Continuous data were compared with unpaired t tests. Based on the univariate analysis we constructed 2 models for the dermoscopic diagnosis of pigmented mucosal lesions. According to the first model, the presence of blue, gray, or white color plus the presence of a structureless zone (even if only parts of the lesions were structureless) was regarded as suspicious. According to the second model, every lesion with blue, gray, or white color was suspicious whether or not a structureless pattern was present. We calculated sensitivities, specificities as well as positive and negative predictive values for both models according to standard formula. All given P values are 2-tailed, and P <.05 indicates statistical significance.

### RESULTS

#### GENERAL DATA

We included 140 pigmented mucosal cases from 92 females (66%) and 48 males (34%). The mean (SD) age of the patients was 45 (18) years. With regard to anatomic site, 76 lesions were located on the lip (54.3%), 32 on the labia majora or minora (22.9%), 15 at the glans (10.7%), 3 at the praepuueum (2.1%), and 14 (10.0%) on other anogenital areas (Table 1). The histopathologic diagnoses included 103 melanotic macules (73.5%), 11 melanocytic nevi (7.9%), 11 melanomas (7.9%) (1 melanoma in situ and 10 invasive melanomas with a Breslow tumor thickness of 0.5-10.0 mm with a minimal clinical length of 4 mm), 8 inflammatory diseases (5.7%), 4 vascular lesions (2.9%), 2 Bowen disease lesions (1.4%), and 1 metastasis (0.7%) (Table 1). Most of the images (117 of 140), including those of all melanomas and the metastasis, were nonpolarized. Patients with malignant lesions were significantly older than patients with benign lesions (mean [SD] age, 60.1 [22.8] years vs 43.2 [17.3] years; P < .001).

#### DERMOSCOPIC PATTERNS AND COLORS

Only 1 pattern was found in 79 lesions (56.4%), 2 patterns in 31 lesions (22.1%), 3 patterns in 23 lesions (16.4%), and 4 patterns in 1 lesion (0.7%).
(16.4%), and 4 patterns in 7 lesions (5.0%). The structureless pattern was found in 81 lesions (57.9%); parallel, reticular, and/or curved lines in 52 lesions (37.1%); circles in 27 lesions (19.3%); globules or clods in 9 (6.4%); and dots in 14 lesions (10.0%). A summary of the frequencies of patterns by anatomic site is given in Table 2.

We found 86 lesions with only a single color (61.4%), 40 lesions with 2 colors (28.6%), 12 lesions with 3 colors (8.6%), and 2 lesions with 4 colors (1.4%). The most frequent color was brown, which was present in 126 lesions (90.0%), followed by gray (44 lesions [31.4%]), blue (15 lesions [10.7%]), white (11 [7.9%]), red (10 [7.1%]), black (7 [5.0%]), and purple (1 [0.7%]). A summary of the frequencies of colors by anatomic site is given in Table 2.

### PATTERNS AND COLORS BY DIAGNOSIS

We performed 2 separate analyses. In the first one, we compared the dermoscopic features of the 126 benign lesions with all melanomas (n = 11) and in the second one with all malignant lesions (n = 14, adding 2 cases of Bowen disease and 1 metastasis). With regard to patterns, only the presence of structureless zones was significantly associated with malignant lesions. Structureless zones were found in all malignant lesions but only in 53.2% of benign lesions (P = .03 for benign lesions vs melanoma and P = .02 for benign vs malignant lesions). With regard to colors, a significant difference between benign and malignant lesions was found for blue, gray, and white, and for the number of colors (see Table 3 for P values both analyses).

Based on the results of the univariate analysis we established 2 simple diagnostic models for the diagnosis of pigmented mucosal lesions by dermoscopy: according to the first model, the presence of blue, gray, or white color plus the presence of a structureless zone (even if only parts of the lesion were structureless) was regarded as suspicious. With regard to the diagnosis of melanoma, this model had a sensitivity of 100%, a specificity of 92.2%, a positive predictive value of 32.4%, and a negative predictive value of 100%. Pertaining to the diagnosis of any malignant lesion, the sensitivity of this model was 92.9%; the specificity, 83.3%; the positive predictive value, 38.2%; and the negative predictive value, 90.1%. In the second model we used only colors. Every lesion that contained blue, gray, or white color was regarded as suspicious, irrespective of the pattern. The sensitivity for melanoma of this model was 100%; the specificity, 64.3%; and the positive predictive and negative values, 19.3% and 100%, respectively. With respect to the diagnosis of any malignant tumor the sensitivity of the second model was 92.9%; the specificity, 65.1%; the positive predictive value, 22.8%; and the negative predictive value, 98.8%.

### COMMENT

This multicenter, retrospective, observational study of 140 cases by the IDS revealed that the presence of blue, gray, or white color is the strongest clue in differentiating between malignant and benign mucosal lesions by dermoscopy. The combination of at least 1 of the 3 colors and the presence of structureless zones had a relatively high diagnostic accuracy (Figure 1 and Figure 2).

Multicomponent patterns were found in 6 of 8 mucosal melanomas in the monocentric study of Lin et al, and in 3 of 5 vulvar melanomas in the study by Ronger-Salve et al. These authors did not report on how many of these multicomponent lesions contained structureless zones. A structureless pattern—at least in parts of the lesion—was seen in all malignant tumors in our study but only in 53.2% of the benign lesions. If a benign lesion was structureless, its color was usually brown but did not include blue, gray, or white. The presence of homogeneous areas was described by Lin et a in 25% of the malignant and benign lesions and by Ronger-Salve et al in 22%. Mannone et al found 10 of 11 vulvar melanosis to be structureless, and Virgili et al found a homogeneous pattern in 6 of 8 vulvar melanocytic nevi. However, the term homogeneous is misleading in the sense that it is unclear whether it refers to homogeneity of structure or color or both. Structureless is clearly defined as the absence of any discernible structure (dots, globules or clods, circles, or lines), irrespective of color. In our study, dots were detectable in 28.6% of the malignant lesions and in 7.9% of the benign lesions. In the investigation of Lin et al, no dots were seen in the melanomas but were noted in 25% of the benign lesions. Mannone et al did not describe dots in their study.

To our knowledge, no systematic analysis of the colors of the mucosal lesions in dermoscopy has been published to date. The blue veil of malignant melanomas...
Pigmented and nonpigmented lesions of the mucosa are rare, but they have a wide range of possible diagnoses. Therefore, it is a challenge to differentiate between benign and malignant tumors. The dermoscope can be used with a sterile transparent protection if the anatomical situation allows this.

Most lesions (54.3%) were from the lip, as in the study by Lin et al. In our study, we had a higher percentage of melanotic macules (73.6% vs 60%) and a lower number of malignant neoplasms (10% vs 22%) compared with the findings by Lin et al. According to the classification by Kittler and Kittler et al, we identified 5 different patterns and 7 different colors. Lin et al identified 7 patterns. However, the different numbers and definitions of patterns between the the present study and the study by Lin et al do not actually reveal different patterns. The pattern we termed structureless Lin et al named homogeneous; what we call globules or clods they referred to as dotted-globular; we use the terms circles, lines, and fish-scale and they used ringlike, finger-print, and hyphal, respectively. The multivariate pattern described by Lin et al corresponds to lesions with multiple patterns in our study. However, the results of our study show that multiple colors are a better clue to malignant lesions than multiple patterns.

Lin et al also analyzed different dermoscopic algorithms, which revealed a sensitivity of 63% to 100% in the 8 melanomas. The specificity in the 32 benign lesions ranged from 94% to 100%. As for dermoscopic findings of the nail unit, we do not encourage the use of the first step of the 2-step algorithm to differentiate between melanocytic and nonmelanocytic lesions. Most mucosal pigmented lesions are nonmelanocytic (melanocytic macules) and would be incorrectly classified as melanocytic. Compared with the question of whether a lesion is benign or malignant, the question of whether a lesion is melanocytic or nonmelanocytic is of minor importance. The critical decision is whether to perform a biopsy. Consequently, none of the established dermoscopic algorithms were used in our study. The analysis of pattern and colors as demonstrated has a high diag-

Table 3. Patterns and Colors Correlating to Melanoma, Malignant Tumors (Melanoma, Bowen Disease, and Metastasis), and Benign Lesions

<table>
<thead>
<tr>
<th>Pattern or Color</th>
<th>Melanoma (n=11)</th>
<th>Malignant Tumors (n=14)</th>
<th>Benign Lesions (n=126)</th>
<th>Analysis 1</th>
<th>Analysis 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structureless</td>
<td>11 (100)</td>
<td>14 (100)</td>
<td>67 (53.2)</td>
<td>.03</td>
<td>.02</td>
</tr>
<tr>
<td>Lines</td>
<td>6 (54.5)</td>
<td>6 (42.9)</td>
<td>46 (36.5)</td>
<td>&gt;.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Parallel</td>
<td>1 (9.1)</td>
<td>1 (7.1)</td>
<td>26 (20.6)</td>
<td>&gt;.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Reticular</td>
<td>3 (27.3)</td>
<td>3 (21.4)</td>
<td>10 (7.9)</td>
<td>&gt;.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Curved</td>
<td>1 (9.1)</td>
<td>1 (7.1)</td>
<td>18 (14.3)</td>
<td>&gt;.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Circles</td>
<td>1 (9.1)</td>
<td>1 (7.1)</td>
<td>26 (20.6)</td>
<td>&gt;.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Globules/clods</td>
<td>0</td>
<td>1 (7.1)</td>
<td>8 (6.3)</td>
<td>&gt;.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Dots</td>
<td>4 (36.4)</td>
<td>4 (28.6)</td>
<td>10 (7.9)</td>
<td>.34</td>
<td>.68</td>
</tr>
<tr>
<td>Patterns, No.</td>
<td>1</td>
<td>4 (36.4)</td>
<td>6 (42.9)</td>
<td>.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 (9.1)</td>
<td>2 (14.3)</td>
<td>&gt;.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4 (36.4)</td>
<td>4 (28.6)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2 (18.2)</td>
<td>2 (14.3)</td>
<td>.05</td>
<td>.02</td>
</tr>
<tr>
<td>Color</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown</td>
<td>8 (72.7)</td>
<td>10 (71.4)</td>
<td>16 (12.7)</td>
<td>&gt;.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Black</td>
<td>1 (9.1)</td>
<td>1 (7.1)</td>
<td>6 (4.8)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blue</td>
<td>8 (72.7)</td>
<td>8 (57.1)</td>
<td>7 (5.6)</td>
<td>&gt;.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Grey</td>
<td>8 (72.7)</td>
<td>10 (71.4)</td>
<td>34 (27.0)</td>
<td>.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Red</td>
<td>3 (27.3)</td>
<td>3 (21.4)</td>
<td>7 (5.6)</td>
<td>.51</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Purple</td>
<td>0</td>
<td>1 (7.1)</td>
<td>1 (0.8)</td>
<td>&gt;.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>White</td>
<td>4 (36.4)</td>
<td>5 (35.7)</td>
<td>6 (4.8)</td>
<td>.07</td>
<td>.03</td>
</tr>
<tr>
<td>Colors, No.</td>
<td>1</td>
<td>0</td>
<td>2 (14.3)</td>
<td>&gt;.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3 (27.3)</td>
<td>3 (21.4)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>7 (63.6)</td>
<td>8 (57.1)</td>
<td>.05</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1 (9.1)</td>
<td>1 (7.1)</td>
<td>.07</td>
<td>.03</td>
</tr>
</tbody>
</table>

P-values for multiple comparisons. Adjusted P values greater than .99 were rounded.

The overall P values for are given for this variable. Individual P values were not calculated.

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nostic accuracy for any kind of malignant tumor that is at least in the range of the observation by Lin et al.13

The age of the patient could also be helpful in the diagnostic dilemma of pigmented lesions of the mucosa: mucosal melanomas are more common in older patients, as we have shown in our study (mean age, 43.2 years for patients with benign pigmented lesions vs 60.1 years for those with mucosal melanomas).59 However, age should be considered carefully because our youngest patient was 16 years old and had a melanocytic lesion of uncertain malignant potential. In addition, mucosal melanomas are more frequent in the non-Hispanic white population than in Asian or black populations.21

Our study has several limitations. We evaluated the lesions in consensus, and we did not calculate the interobserver agreement. This could be performed in a fol-

Figure 1. Pigmented lesions. A, Pigmented lesion at the upper lip of a 25-year-old female patient. Inset: Dermoscopic image shows a benign macula with structureless pattern and brown color. B, Pigmented lesion on the genitals of a 23-year-old female patient. C, Dermoscopy demonstrates a benign macula with parallel lines, circles, and brown color. D, Pigmented lesions at the prepuce and glans penis of a 37-year-old patient. E, Dermoscopy shows benign macules with structureless pattern and brown color.
low-up study with different raters. Another more important limitation is the fact that most melanomas in our sample were already relatively large. Most of them were easy to diagnose clinically. Criteria of small mucosal melanomas may differ from those that we described. The challenge is to detect any malignant lesion in an early stage and also in mucosal melanomas. Very little is known about the growth pattern of the mucosal melanoma at present. Only case reports are available to approach this problem. Betti et al described a prominent, wide, and irregular pigmented network, which stopped abruptly at the periphery of a melanoma in situ. One of our included melanocytic lesions of uncertain malignant potential showed the presence of structureless zones and asymmetric parallel lines that looked like pseudopods with black and very distinct gray and blue colors. An early invasive melanoma of the vulva with a Breslow tumor thickness of 0.5 mm described by de Giorgi et al had a nonhomogeneous appearance with gray and blue colors and a whitish veil. In a melanoma of our study with the same tumor thickness and in the same location, a structureless pattern, reticular lines, and brown, gray, and blue colors were detectable (Figure 3). Early signs of a melanoma of the mucosa could include the presence of structureless parts and gray color. Additional late-stage signs in larger lesions could include the presence of multiple patterns and additional colors, especially blue or white. To answer the question of the diagnostic dilemma of pigmented lesions of the mucosa, follow-up studies of mucosal lesions would be helpful, but the realization of such studies could be very difficult in the clinical setting. However, a biopsy or excision biopsy of a doubtful mucosal lesion in dermoscopy is the gold standard at present.

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Author Contributions: Drs Blum, Simionescu, and Kittler had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Blum. Acquisition of data: Blum, Simionescu, Argenziano, Braun, Cabo, Eichhorn, Kirchesch, Malvehy, Marghoob, Puig, Ozdemir, Stolz, Tromme, Weigert, Wolf, Zalaudek, and Kittler. Analysis and interpretation of data: Blum, Simionescu, and Kittler. Drafting of the manuscript: Blum, Simionescu, and Kittler. Critical revision of the manuscript for important intellectual content: Argenziano, Braun, Cabo, Eichhorn, Kirchesch, Malvehy, Marghoob, Puig, Ozdemir, Stolz, Tromme, Weigert, Wolf, and Zalaudek. Statistical analysis: Kittler.

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