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The Complexity of Diagnosing Melanoma

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Recognizing that a cure lies in timely detection, dermatologists strive to diagnose malignant melanoma (MM) at the earliest possible stage. The desire to achieve this goal without injudiciously and unnecessarily excising many benign lesions has led to numerous techniques that assist clinicians in differentiating nevi from MM, including clinical mnemonics and algorithms, optical imaging instruments, and computer-assisted diagnostic systems. Most of these seemingly diverse methods rely on evaluating the *in vivo* morphology of lesions. In this issue, Guitera *et al.* compare dermoscopy with reflectance confocal microscopy (RCM) in an attempt to determine which imaging modality facilitates accurate diagnosis of melanocytic lesions using diagnostic parameters such as sensitivity and specificity.

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The study by Guitera *et al.* (2009, this issue) is an important step toward future use of RCM as a "bedside" diagnostic tool. At this juncture, we reflect on the framework of the clinical diagnosis of melanocytic lesions and where *in vivo* imaging tools fit into this framework. Although Guitera *et al.* have shown that RCM increased diagnostic accuracy over dermoscopy, such a comparison may be an oversimplification of what occurs in real life. Components of skin examination and diagnostic aids are not mutually exclusive; rather, they provide complementary information necessary for rendering a correct decision. For example, in the study by Guitera *et al.*, eight MMs that were misdiagnosed via RCM were correctly diagnosed with dermoscopy. On the other hand, 12 MMs that were incorrectly identified with dermoscopy were correctly diagnosed via RCM. When dermoscopy and RCM were used together, sensitivity was highest, with only three melanomas incorrectly classified.

To judge whether an *in vivo* diagnostic technique is truly superior in terms of diagnostic accuracy, it is essential to account for the complexity of the clinical decision-making process. Components of the skin examination used in the evaluation of lesions include patient-derived anamnestic data, analytical reasoning, comparative recognition, differential recognition, and pattern analysis, which is also known as gestalt (see Figure 1; Gachon *et al.*, 2005). This information can then be integrated with information obtained via diagnostic tools such as dermoscopy and RCM. In fact, experts "use multiple, combined strategies to solve clinical problems, suggesting a high degree of mental flexibility and adaptability in clinical reasoning" (Norman, 2006). Experts' ability to rapidly extract pertinent information from multiple sources has proven difficult for automated vision instruments to recreate. Thus, it is the evolving human cognitive process that allows clinicians to identify MM despite its varied clinical faces.

The ABCD mnemonic, introduced in 1985, represents an analytical method for the evaluation of MM and was probably the first method conveyed by experts to the dermatological community and later to the general public. However, the ABCD method did not help to distinguish some dysplastic nevi from MMs and failed to identify some MMs at an early stage (e.g., MMs with a small diameter). The introduction of analytical algorithms that utilize dermoscopy—such as the ABCD method of dermoscopy, the seven-point checklist, and the Menzies method—have improved discrimination but have not eliminated the challenge of clinically distinguishing MMs from some nevi (Roesch *et al.*, 2006).

In 1990, patient anamnestic data, which included both historical criteria (i.e., the presence of new or changing lesions) and lesion symptomology, were emphasized to help detect MM. Such patient-derived information was sensitive for MM identification and allowed the detection of an additional subset of MM that defies the ABCDs. Thus was born the Glasgow checklist. Similarly, "E," for evolution, was subsequently added to the ABCD mnemonic. However, patient self-reporting has limitations, and the need to further improve the detection of new and changing lesions brought about the introduction of baseline whole-body photography and short-term dermoscopic mole monitoring in clinical practice—both of

> RCM increases specificity above dermoscopic assessment alone.

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Table 1. General scheme of clinical approach to pigmented lesions

Level of diagnosis	Relevant signs, mnemonics, and algorithms	Comments
Level 1, "macro": whole-body screening	Patient history (Glasgow seven-point checklist) Context: patient age and anatomical location of lesion "Ugly Duckling" vs. "moles breed true": differential recognition WBP: comparative recognition	Saccade (scanning) vision is active Main determinant of sensitivity
Level 2, "micro": individual lesion assessment	Analytical criteria (ABCD mnemonic, ABCD rule of dermoscopy, Menzies method, seven-point checklist of dermoscopy) Pattern analysis at the clinical and dermoscopic levels RCM Short-term mole monitoring	Saccade vision is suppressed Focused vision (light focused on fovea, allowing for sharp color vision) is active Main determinant of specificity

ABCD, asymmetry, borders, color, diameter—criteria for assessment; WBP, whole-body photography; RCM, reflectance confocal microscopy.

which rely on our comparative image-recognition process. The underlying premise of change as a sensitive sign for MM diagnosis is that MMs tend to be more biologically dynamic than nevi, even over as little as a 3-month period of follow-up (Altamura *et al.*, 2008).

Another milestone in MM detection was the acknowledgment of the importance of differential recognition processes. In 1998, Grob and Bonerandi (Grob *et al.*, 1998) described the "ugly duckling" sign for MM detection. This clinical sign emphasizes that it is imperative that we not only evaluate the morphology of the lesion in question but also compare it with the surrounding moles. Outlier lesions that look different from surrounding nevi tend to attract our attention, and some of these lesions do indeed prove to be MMs (Scope *et al.*, 2008). Although the ugly-duckling sign is usually applied to unaided clinical evaluation, it has the potential to be utilized in dermoscopic evaluation because individuals also tend to harbor a limited number of dermoscopic patterns in their nevi, a concept known as "moles breed true" (Scope *et al.*, 2006). Thus, the ugly-duckling sign and moles-breed-true concept are two sides of the same coin, namely, the differential recognition process of isolating lesions that are morphologically different from the common denominator. This concept can be broadened over the aforementioned parameters of change and symptoms; although change in nevi is not uncommon, MMs will change differently than nevi and may produce unique symptoms and signs that prompt MMs to be singled out (Banky *et al.*, 2005).

No one has been able to peer into experts' brains to determine exactly how they analyze pigmented lesions. However, some insights are becoming apparent (Montgomery, 2006). We believe the following may constitute an overall scheme (summarized in Table 1). In patients with numerous moles, we try to identify suspicious lesions by patient history of change or symptoms, comparison with baseline images, and the search for an outlier lesion that looks different from the neighboring moles (i.e., the ugly-duckling sign). Once a suspect lesion has been identified, we use naked-eye clinical examination; if more information is needed, we may employ a magnifying lens or a dermatoscope. If the overall appearance of the lesion is recognized as a benign pattern, we move on. On the other hand, if the overall pattern fits the gestalt of a clear-cut MM, we opt for surgical removal. In cases where the pattern cannot be easily categorized as either benign or malignant, we may use analytical criteria (e.g., search for melanoma-specific dermoscopic structures).

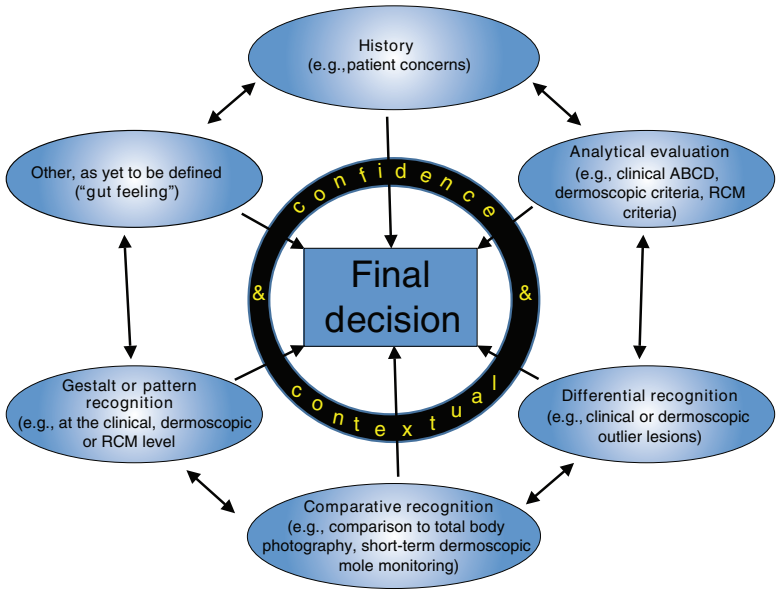

Figure 1. The final decision of whether to biopsy a lesion is not simple. The main components of this cognitive process involve differential recognition (e.g., the "Ugly Duckling sign"), analytical recognition (e.g., the "Little Red Riding Hood sign," Mascaro *et al.*, 1998), pattern recognition (e.g., the "Beauty and the Beast sign," Marghoob *et al.*, 2007), and comparative recognition. All of these processes occur on the clinical level, but they can be augmented by tools such as dermoscopy and RCM. Admittedly, there is probably more complexity to decision making than depicted. Personality attributes such as experience and contextual factors such as time pressure may influence the process. Finally, there are cognitive processes not yet scientifically identified but generically referred to as "gut feelings." ABCD, asymmetry, borders, color, diameter—criteria for assessment. RCM, reflectance confocal microscopy.

However, if we are still unable to find conclusive criteria for differentiating the lesion as benign or malignant, we may opt to gather more information. RCM may provide additional diagnostic information because of the ability to view tissue with cellular resolution with thin optical sections from the level of the stratum corneum to the papillary dermis. Based on the integration of all the aforementioned examination methods and diagnostic tools, we decide whether the lesion must be surgically removed or followed using techniques such as short-term mole monitoring to further assess its biological nature.

It is clear from the study by Guitera *et al*. (2009, this issue) that RCM significantly increases specificity beyond that of dermoscopic assessment because it adds new features that help to correctly diagnose many dermoscopically equivocal lesions as nevi, including those that are pink or lightly pigmented. Such an increase in specificity should ultimately translate into a decrease in unnecessary surgical removal of many nevi. However, the ultimate goal is not to overlook MM (i.e., the goal is to increase sensitivity). Has this been achieved in this study? As mentioned above, dermoscopy and RCM together enabled the researchers to correctly identify more MMs, albeit not 100% of MMs in the study. Yet one may argue that the true sensitivity for the diagnosis of lesions in this study, or in any study based on excised lesions, is actually 100%, because all MMs in this study were actually removed by the clinicians, probably based on the complex clinical decision-making process rather than dermoscopy, RCM, or both. In fact, no study today tries to measure the real-life sensitivity for MM detection because that would require either removing all skin lesions for histopathological analysis, including those that appear clinically banal, or following patients for many years to ensure that absolutely no MMs were missed.

Even after a complete skin examination in a systematic manner, some MMs may appear banal and may be simply overlooked, whereas others may initially catch our attention but be erroneously dismissed as benign. The various components of the examination (e.g., patient history, assessing for outlier lesions) and diagnostic aids (such as dermoscopy and RCM) may be viewed as complementary "filters" that help catch MM. Another safeguard against "missed" MM is periodic patient examinations. These examinations provide an additional opportunity for the patient to pass through our filters, allowing us to monitor changes that may have developed in the MM during the elapsed interval.

MM detection is complex. The search for more robust methods to diagnose it has helped us recognize the many faces of this malignancy, some of which would probably have escaped detection were it not for our increased knowledge. For example, light-colored MMs are often difficult to diagnose. However, based on the study by Guitera *et al.*, RCM may prove to be beneficial in correctly identifying these lesions. As stated by the philosopher Goethe, "The eyes see only that which the mind is prepared to comprehend." From the beginning of time, MMs have had colors, structures, and patterns for all to see; however, "some see but do not comprehend" (Davis, 1978). The pursuit of the ever-elusive "perfect" method to detect MM continues to enrich our ability to recognize many MMs that would have been missed in the past. There is a subset of MMs that can be diagnosed only by patient history, some that can be diagnosed instantly "from the examination room doorway" by gestalt, and others that require a combination of analytical, differential, and comparative recognition. This process is enhanced by instruments such as the magnifying lens or dermoscope. Now, with RCM, we have a new tool to add to our armamentarium.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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