Strategies for early melanoma detection: Approaches to the patient with nevi
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Given its propensity to metastasize and the lack of effective therapies for most patients with advanced disease, early detection of melanoma is a clinical imperative. Although there are no noninvasive techniques for the definitive diagnosis of melanoma, and the “gold standard” remains biopsy with histologic examination, a variety of modalities may facilitate early melanoma diagnosis and the detection of new and changing nevi. This article reviews the general clinical principles of early melanoma detection and various modalities that are currently available or on the horizon, providing the clinician with an up to date understanding of management strategies for their patients with numerous or atypical nevi. (J Am Acad Dermatol 2009;60:719-35.)

Learning objective: After completing this learning activity, participants should understand the clinical importance of early melanoma detection, appreciate the challenges of early melanoma diagnosis and which patients are at highest risk, know the general principles of early melanoma detection, be familiar with current and emerging modalities that may facilitate early melanoma diagnosis and the detection of new and changing nevi, know the advantages and limitations of each modality, and be able to practice a combined approach to the patient with numerous or clinically atypical nevi.

Melanoma has doubled in incidence in recent decades and is increasing more rapidly than any other cancer.1 There are an estimated 60,000 cases and more than 8000 deaths associated with melanoma in the United States annually, with an average individual lifetime risk of melanoma approaching 1 in 75.2 Despite considerable efforts to develop new therapies for melanoma, patients with advanced disease continue to have a poor prognosis.3 Although many patients with melanoma localized to the skin are cured by surgical excision, increased time to diagnosis is associated with a higher stage of disease, and those with regional lymphatic or metastatic disease respond poorly to conventional radiation and chemotherapy, with 5-year survival rates ranging from 10% to 50%.3 The cost of treating melanoma rises significantly with disease stage; less than 20% of patients with stage III and stage IV disease were responsible for 90% of the total annual cost for treating melanoma in 1997, which was estimated at $563 million.4 Earlier detection of melanoma is a key factor in improving patient survival and decreasing treatment costs.

There is currently no consensus in our specialty regarding the optimal modality or strategy for early melanoma detection. While isolated lesions can be biopsied, this becomes problematic in patients with numerous nevi or large clinically atypical nevi. In a recent survey of fellows of the American Academy of Dermatology regarding their management of patients with history of histologically-confirmed dysplastic nevi, Tripp et al5 reported that 99% recommended self-examinations, 75% performed total body skin

Abbreviations used:
CSLM: confocal scanning laser microscopy
DELM: digital epiluminescence microscopy
OCT: optical coherence tomography
RCM: reflectance-mode confocal microscopy
RTI: reflex transmission imaging
SIA: spectrophotometric intracutaneous analysis (SIAscope)
SSE: self-skin examination
creased risk for melanoma is cost-effective, as is Annual screening of patients known to be at increased risk. Classical risk factors for melanoma include previous personal history of melanoma, possession (or history of) atypical/dysplastic nevi,8-10 Patients with a history of a second melanoma have a 5% to 8% risk of developing a third melanoma.11,12 With respect to nevi, Holly et al13 reported relative risks of 1.6 for patients with 11 to 20 nevi, and 9.8 for ≥ 100 nevi, and relative risks of 3.8 for 1 to 5 atypical nevi and 6.3 for ≥ 6 atypical nevi. Additional risks are associated with having fair skin (4-fold), red hair and blue eyes (2-fold),15 a history of nonmelanoma skin cancer (2-3 fold),16,17 and a history of sunburns or excessive ultraviolet light exposure (2-fold).18 including indoor tanning (2-3 fold).19 Other important aspects to consider are age and sex, because risk increases with age, men have a higher incidence of melanoma than women,20 and changing or new nevi are more likely to be melanoma in patients over 50 years of age.21 All of these risk factors can be assessed by history and a physical examination. Annual screening of patients known to be at increased risk for melanoma is cost-effective, as is one-time screening of the general population over 50 years of age and biannual screening of siblings of melanoma patients.23 Several studies have shown that screening is associated with detection of thinner melanomas.24-26

### Obstacles to screening

Although campaigns such as "Melanoma Monday" sponsored by the American Academy of Dermatology have increased public awareness, an insufficient number of dermatologists26,29 and the lack of time for skin cancer screening by practicing dermatologists40 remain real obstacles to adequate melanoma screening and may account for delayed diagnosis. While primary care physicians could fill some of this gap, they are less likely to perform complete skin examinations and, according to several studies,29,32 are less likely than dermatologists to correctly diagnose melanoma. In addition, melanomas biopsied by other physicians were associated with greater depth and increased mortality than those biopsied by dermatologists.35,34

Several studies have also shown that delays in melanoma diagnosis may be attributed to patient-related factors, such as a lack of concern.35,36 Males, the elderly, and those of lower educational status tend to have poorer rates of self-detection, longer delay before seeking medical attention, and greater melanoma tumor thickness.37,38

### WHAT WE TELL PATIENTS

#### Recognizing melanoma

The ABCD acronym was devised in 1985 by Kopf and colleagues39 to help patients recognize several clinical features of melanoma: asymmetry, border irregularity, color variation, and diameter (≥6 mm). While most melanomas tend to exhibit these features, amelanotic melanomas usually do not, and therefore their diagnosis is often delayed.40,41 In addition, melanomas arising de novo (not within preexisting nevi) will be smaller than 6 mm at an early stage. The acronym is also not very specific; seborrheic keratoses, which are very common in older patients, often will exhibit "ABCD" features.

The history of change in a nevus is a red flag that may signal malignancy, and is noted at a significantly higher frequency in malignant than benign pigmented skin lesions.10 Indeed, short-term monitoring studies have revealed that most growing melanomas exhibit observable changes over a period of 3 to 6 months.43-45 Longer-term observational studies similarly found that melanomas tend to exhibit nonuniform growth patterns.46 Certain changes in nevi are associated with earlier melanoma detection, including changes in color, size, shape, elevation, and

### Table I. Goals for monitoring and early melanoma detection

<table>
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<tr>
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patient symptoms, such as itching.\textsuperscript{17} Given these considerations, Abbasi et al\textsuperscript{48} and Rigel et al\textsuperscript{49} recommend adding an “E” for evolving to the ABCD acronym to increase its sensitivity and specificity.

**New and changing nevi**

Not all changes in nevi, however, are suspicious for melanoma. This is particularly true if the change is symmetric enlargement, which is expected as moles grow (particularly in younger patients). Other normal changes include uniform darkening of nevi, which may occur following sun exposure.\textsuperscript{50} Rates of change in nevi have been reported in the range of 4% to 6%,\textsuperscript{51-53} and we recently reported that only 96 of 5945 (1.6%) clinically atypical nevi exhibited interval changes over a 4-year monitoring period.\textsuperscript{54} Therefore, spontaneous changes in nevi that are not attributed to other factors (see below) are uncommon in adults.

Although changes in nevi during pregnancy are thought to be common,\textsuperscript{55} there is little supporting evidence in the literature. Sanchez et al\textsuperscript{56} found that of 389 pregnant women examined, only 10% reported changes in their pigmented lesions and that none of 28 lesions biopsied revealed significant histologic changes compared with similar pigmented lesions from age-matched women who were not pregnant. Pennoyer et al\textsuperscript{57} compared sizes of 129 nevi on the back in 22 pregnant women during their first and third trimesters and did not find significant interval changes in nevus size. Akturk et al\textsuperscript{58} evaluated 97 nevi in 56 pregnant women in the first and third trimesters and did not find significant increases in average nevus diameter, but predominantly in lesions on the front of the body. Approximately 6% of lesions developed dermatoscopic changes, again predominantly on the front of the body.\textsuperscript{59} Zampino et al\textsuperscript{60} monitored 86 nevi located on the back in 47 pregnant women, and found significant progressive lightening of nevi without significant changes in size. Taken together, these studies suggest that changes in nevi during pregnancy are relatively uncommon and may largely result from skin expansion.

Nevi may also undergo reversible changes in color or texture that may be incited by chronic rubbing or other trauma. It is important to recognize that these types of changes are generally symmetric and uniform, while asymmetric changes in shape or color within a changing lesion, including ulceration or bleeding, would be suspicious for melanoma. It is suggested that morphologic changes in nevi subjected to mechanical irritation are caused by increased numbers of suprabasal melanocytes and alterations in keratinocyte adhesion molecules.\textsuperscript{60} Selim et al\textsuperscript{61} examined 92 (nonsurgically) traumatized nevi and in 20% noted pagetoid spread, almost always directly beneath zones of parakeratosis; cytologic atypia and mitoses in melanocytes were rarely seen.

Similarly, a new nevus may not be concerning, unless it appears different than the patient’s other existing nevi. New moles are expected in younger patients,\textsuperscript{62} and it is well known that the total nevus number generally peaks in the third decade of life before slowly declining in the seventh and eighth decades.\textsuperscript{63} Nevi may also regress in younger patients, as Siskind et al\textsuperscript{64} found in monitoring 230 facial nevi in 20 adolescents over a 4-year period. Although total nevus number increased by 56%, 61 nevi (27%)—predominantly small, flat lesions—disappeared.\textsuperscript{64} In our practice, we have documented that it is not uncommon for “nevogenic” patients to develop new nevi into their 40s and 50s. In addition, new nevi may arise in “eruptive” fashion in several clinical contexts. These include blistering skin diseases, such as erythema multiforme,\textsuperscript{65} toxic epidermal necrolysis,\textsuperscript{66} and epidermolysis bullosa.\textsuperscript{67} Eruptive nevi have also been described in immunosuppressed patients following organ transplantation\textsuperscript{68} and HIV infection.\textsuperscript{69} Finally, it is important to note that only a small percentage of new or changing lesions will represent melanoma, although the likelihood increases significantly if the patient is over 50 years of age.\textsuperscript{21}

**Role of self-skin examination**

Instructing patients to perform regular SSEs is important for several reasons. First, melanomas are commonly detected by patients, although it is far more common for dermatologists to detect second primary tumors.\textsuperscript{33,70,71} Performing a SSE has been associated with thinner melanomas\textsuperscript{25} and reduced mortality\textsuperscript{72} in some studies, although others found that patient-detected melanomas are more likely to be thicker than those detected by physicians.\textsuperscript{70,71} One study showed 58% sensitivity and 62% specificity for patient detection of artificial changes in mole size.\textsuperscript{73} However, the diagnostic accuracy of SSEs can be improved with the use of digital photography.\textsuperscript{74,76}

Second, the SSE may be the only defense for patients who develop nodular melanomas which, because of their rapid growth, are more likely to arise between physician screening visits.\textsuperscript{30,77} Finally, SSEs are important because they establish a role for the patient in sharing responsibility with the physician in early melanoma detection. Patients should initially be advised to perform SSEs frequently so as to become familiar with the appearance of their nevi, and then transition to monthly SSEs to detect new and changing nevi. After the initial period, the monthly frequency for SSEs seems optimal given
the interval of clinical changes in developing melanomas (3-6 months, as noted above). If a SSE is performed too frequently, patients may not appreciate small or gradual changes over time.

**VISUAL DETECTION**

In some cases, particularly with more advanced lesions, melanoma can be easily diagnosed with the naked eye. More commonly, however, we are faced with the difficult clinical differential diagnosis of atypical nevus versus melanoma. In addition, benign-appearing amelanotic melanomas are easily missed. Multiple studies based on test photographs and retrospective analyses have estimated the success rate of dermatologists in correctly diagnosing melanoma at approximately 80%, although diagnostic accuracy in practice likely varies depending on the years of experience and frequency of patients seen with pigmented lesions. Although physicians are able to detect melanoma at earlier stages than their patients, multiple studies have shown that dermatologists are better than other physicians at early detection. Initial melanomas found by dermatologists are more likely to be ≤ 0.75 mm in depth than those found by other physicians and are therefore associated with better survival rates and lower cancer-related mortality.

**Should we focus on nevi?**

Melanomas are often described by patients as a “new mole.” As noted above, the presence of nevi is associated with increased (2- to 10-fold) melanoma risk. However, the annual risk of transformation to melanoma for a single nevus is estimated at only 1 in 200,000, raising the question of whether nevi are truly precursors of melanoma or simply a marker of melanoma risk. Given that 22% to 50% of melanomas show nevus origin histologically, it is likely that both scenarios are true. A recent study comparing nevus-derived and de novo melanomas did not find a significant difference in tumor thickness when controlling for other prognostic factors. It is reasonable to conclude that at least half of melanomas arise de novo, from isolated melanocytes rather than from preexisting nevi, and therefore effective approaches to early melanoma detection ideally should identify and evaluate both new and changing nevi.

**Signature nevi**

Before the close visual inspection of a particular nevus, it is useful to first look for other lesions on the patient that display similar morphologic characteristics. Similar-appearing nevi, or recurring patterns within nevi, constitute a patient’s “signature” lesions. Common nevus signatures include uniformly brown nevi, and uniformly pink nevi in patients with fairer skin types. “Two-tone” nevi are represented by pink or light brown lesions with darker centers or darker lesions with more lightly pigmented centers. The “fried egg” nevus contains a central portion that is elevated. These usually reveal benign histologic patterns, although mild dysplasia may be seen. Schaffer et al were the first to use the term “signature nevus,” and have described several of the less common varieties. “Eclipse” nevi display central tan or pink coloration with a darker peripheral rim, and are commonly found on the scalp in children. An inverse clinical pattern may also be seen, with darker central coloration and a lighter peripheral rim. Targetoid or “cockade” nevi exhibit concentric patterns of pigmentation usually consisting of central and peripheral pigmented areas with an intervening area of hypopigmentation. “Halo” nevi are in various stages of regression because of inflammation, and most commonly present as hypopigmented skin surrounding a pigmented lesion that progressively lightens over time, although darkening of the central lesion has also been described.

Nevi may display eccentric dark dots which can represent epidermal or dermal pigmentation or a clonal nevus. In their prospective analysis of 59 nevi with foci of hyperpigmentation, Bolognia et al found that most were benign but that three lesions (5%) revealed melanoma. Nevi may also contain dark dots at the periphery, or more commonly scattered within the lesion (“shrapnel” or “ladybug” pattern). Perifollicular hypopigmentation may be associated with either terminal or vellus hairs within a nevus. The pattern of hypopigmentation will be circular if the hair is located within the nevus and notched (making the border irregular) if the hair is at the edge of the nevus. Perifollicular hyperpigmentation within nevi has also been described. Although the presence of terminal hairs within a nevus is generally thought to be a benign sign, exceptions have been described. The presence of numerous small uniformly dark nevi constitutes the “cheetah” phenotype. Finally, the “ink-spot lentigo” is technically not a nevus, but refers to a reticulated black solar lentigo that appears to resemble a very dark spot of ink on the skin. These are often seen on a background of numerous or confluent lentigines. These signature lesion types are summarized in Fig 1.

Importantly, these signature patterns generally do not reveal significant melanocytic atypia, but rather represent “biologically benign” explanations for irregularities in nevus pigmentation. Features of signature nevi can be appreciated without magnification. When examining a patient with multiple
clinically atypical nevi, the recognition of signature lesions allows one to narrow down the number of lesions that may need further examination. Bolognia\textsuperscript{97} has compared taking this “low power” view to the dermatopathologist who examines a slide first at 4× and 20× magnification before focusing in on particular areas at higher magnification. Signature lesions may span a morphologic spectrum, and their classification need not be confined to the specific types described above. In addition, patients may have more than one type of signature nevus. But once the signature pattern(s) is identified (ie, which lesions go together), one can then determine which remaining lesions fit the pattern and which ones may require biopsy or further examination.

**Ugly duckling sign**

The “ugly duckling” sign is another useful clinical principle that represents the converse of the signature lesion (ie, the lesion that does not go with all the rest). Once the signature nevus and its relatives have been identified, one may be able to appreciate other nevi that are not “part of the family.” Grob and Bonerandi\textsuperscript{98} coined the term in 1998 in their descriptions of two patients with melanoma; in one, the melanoma was a brown-black lesion in a patient with predominantly red-brown nevi, while in the other case the melanoma was a uniformly dark lesion in a patient whose nevi predominantly displayed multiple colors and irregular borders. The ugly duckling nevus can therefore be an atypical nevus in a background of normal-appearing nevi, or a more normal-appearing lesion in a patient with multiple clinically atypical nevi. In our practice, we have also found it useful to appreciate an additional ugly duckling variant: the solitary clinically atypical lesion in a patient with few or no nevi. Gachon et al\textsuperscript{99} reported that for dermatologists, their immediate impression of a lesion frequently

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<td>Pink</td>
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<td>Two-tone</td>
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<td>Eclipse</td>
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<td>Targetoid (“cockade”)</td>
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<td>Halo</td>
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<td>Dark dots</td>
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<td>Perifollicular pigmentation</td>
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<td>Ink spot</td>
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**Fig 1.** Summary of key features of signature nevi.
incorporates an unconscious reference to the ugly duckling sign. Scope et al\textsuperscript{100} found that the ugly duckling sign was highly sensitive for melanoma detection, even for nondermatologists.

**UNIDIMENSIONAL MODALITIES FOR MELANOMA DETECTION**

A number of imaging modalities are currently available that may enhance the clinical examination of individual lesions and decrease physician to physician variability (Fig 2). A comprehensive review of these modalities was published in the Journal in 2003.\textsuperscript{101} We now turn our focus to recent applications of these modalities to early melanoma detection.

**Dermatoscopy**

Dermatoscopy (also known as dermoscopy or epiluminescence microscopy) is a well established
method in which skin lesions are viewed with a magnifier through an oil/gel interface (conventional immersion contact dermatoscopy) or using cross-polarizing light filters (noncontact dermatoscopy). These mediums limit the amount of reflected light, allowing improved and deeper visualization of pigmented and vascular structures. Dermatoscopy used to be more routinely practiced in Europe than in the United States; however, the advent of DermLite handheld products ranging in price from $500 to $1000 (3Gen, LLC, San Juan Capistrano, CA) has greatly expanded the use of noncontact dermatoscopy. Benvenuto-Andrade et al\textsuperscript{102} compared the capabilities of various dermatoscopic techniques and found moderate to excellent agreement for most colors and dermatoscopic structures. However, they concluded that melanin (dots and streaks) appeared darker, blue nevi had more shades of blue, and vessels, red areas, and shiny white streaks (fibrosis) were better visualized with noncontact polarized dermatoscopy; on the other hand, milia-like cysts and comedo-like openings, peppering, lighter colors, and blue-white (regression) areas were better visualized with immersion contact dermatoscopy.\textsuperscript{102}

Dermatoscopy is not diagnostic, but can increase or decrease confidence that a melanocytic lesion is benign or malignant (see below)\textsuperscript{,43,103-105} thereby improving the early detection of melanoma\textsuperscript{106,107} while reducing the need for unnecessary biopsies.\textsuperscript{108,109} The utility of this technique, not surprisingly, depends on the experience of its user.\textsuperscript{110-112} Piccolo et al\textsuperscript{113} reported that dermatologists with 5 years of experience using dermatoscopy had 92% sensitivity and 99% specificity when diagnosing melanoma from dermatoscopic images; compared to 69% sensitivity and 99% specificity when diagnosing melanoma from dermatoscopic images obtained using a remote-head color video camera with a computer algorithm.\textsuperscript{114} Using a dataset of 2430 lesions, Menzies et al\textsuperscript{124} found that SolarScan gave a sensitivity of 91% and specificity of 68% for melanoma, which was comparable to that of experts. SolarScan is not currently available in the United States.

The basic diagnostic strategy in dermatoscopy typically involves a decision tree to guide whether particular lesions should be biopsied (Fig 3). First, a determination is made whether a lesion is melanocytic or not. The presence of pigmented networks, globules, dots, or streaks favors a melanocytic lesion. The second step for melanocytic lesions is to classify them as benign, suspicious, or malignant based on dermatoscopic features using the scoring systems or algorithms noted above. The principles of signature lesion and ugly duckling can also be applied, looking for consistent and variant dermatoscopic features, respectively, among lesions in each patient. Suspicious lesions should be biopsied or closely monitored. Lesions determined to be nonmelanocytic may then be screened for diagnostic features of seborrheic keratosis (milia-like cysts and comedo-like openings), dermatofibroma (central white scar-like patch), blue nevus (homogeneous blue color), angioma (red-blue-black lacunae), and basal cell carcinoma (arborizing vessels and blue-gray globules).\textsuperscript{125} Finally, lesions that do not display any of these characteristic features and do not appear to be melanocytic should be biopsied to rule out amelanotic melanoma. The major pitfall of dermatoscopy is its failure to detect very early or “featureless” melanomas.\textsuperscript{31,126,127} Some practitioners may be discouraged from using dermatoscopy because they feel it is too time-consuming; however, Zalaudek et al\textsuperscript{128} found in a study of patients randomized to receive complete skin examination either with or without dermatoscopy that use of dermatoscopy increased the median examination time by 72 seconds.

**Confocal scanning laser microscopy**

CSLM (also abbreviated CLSM or LSCM) is a non-invasive technique that allows for the real-time in vivo imaging of skin lesions at variable depths in horizontal planes.\textsuperscript{129,130} In CSLM, a low-power laser
A beam in the visible or near infrared range is focused on the skin, then light reflected from this focal point is detected through a pinhole-sized spatial filter. Imaging depth increases with longer wavelengths, and in normal skin extends to the level of the dermis with a maximum depth of 350 to 400 μm. In a process termed “optical sectioning,” a series of sections through the thickness of the specimen are collected, assembled, and evaluated using specialized reconstruction software. CSLM can be used in either fluorescence or reflectance mode; the latter is known as RCM, which is more suitable for clinical applications. Melanocytes appear bright and can be easily visualized because of the capacity of melanin to backscatter the laser light; epidermal keratinocytes can also be seen. Melanocytic cells in nests can be appreciated in nevi, and intraepidermal melanocytes with disorganization of epidermal structure can be seen in melanoma. Several studies have shown that RCM provides good correlation with dermatoscopy and with processed histologic sections. Clinically amelanotic melanoma may also be detected given the presence of melanosomes and rare melanin granules. Gerger et al generated RCM images of 117 melanocytic tumors before biopsy that were then evaluated by five trained observers. They found overall sensitivity of 88% and specificity of 98%, although using the presence or absence of monomorphic melanocytes as a single diagnostic criterion for melanoma increased sensitivity to 98%.

Although RCM represents a rapid noninvasive technique that can aid in the early diagnosis and management of melanocytic lesions, its high cost (approximately $75,000 for Vivascope [Lucid, Inc, Rochester, NY]) currently limits its broader use. One limitation of this technique is strong contrast attenuation and light scattering caused by hyperpigmented or hyperkeratotic lesions. Additional potential uses of CSLM include the imaging of skin lesions and their margins before biopsy and margin detection in freshly excised tumors, including nonmelanoma skin cancers.

**Multispectral digital dermatoscopy and computer-based analysis**

In multispectral digital dermatoscopy, sequences of images taken at different wavelengths (providing information from a range of depths in a lesion) are coupled with computer-based analysis. For each lesion, quantitative data are generated that can be used by the clinician to help decide whether the lesion should be biopsied. This technique offers the advantages of analyzing features indiscernible to the human eye, probing up to 2 mm below the surface, and limiting physician to physician variability. Two technologies have been described: SIAscopy (Astron Clinica, Lake Success, NY) and MelaFind.
The SIAscope is a chromophore imaging system that probes 1- to 2-cm areas of skin using wavelengths of 400 to 1000 nm. After eight narrowband, spectrally-filtered images are obtained, they are calibrated and entered into a series of algorithms to determine the microarchitecture of the underlying skin. SIAscoped measures the amount of collagen, hemoglobin, melanin, and melanin distribution in the epidermis and dermis. This information is presented in the form of maps called SIAscans, which are then interpreted by the clinician. Moncrieff et al found that the presence of dermal melanin, collagen holes, and blood displacement with erythematous blush gave 83% sensitivity and 80% specificity for melanoma detection in 348 pigmented lesions referred for excisional biopsy. The SIAscope may be useful in the assessment of cosmetic interventions to reduce the appearance of aging by modification of skin color.

MoleMate (approximately $8000; Astron Clinica) incorporates SIAscopcy in a diagnostic algorithm specifically developed for use by primary care physicians. As with conventional dermatoscopy, diagnostic accuracy of the SIAscope depends on the experience of the physician interpreting the SIAscans. In addition, hyperkeratosis in seborrheic keratoses can be interpreted as dermal melanin, giving false positive results—ideally, conventional dermatoscopy can be coupled with SIAscopcy to avoid diagnostic pitfalls. A newer version, SIAscope V, provides higher-resolution images and is considered to be superior to the older version (SIAscope II).

MelaFind acquires 10 images for each lesion that encompass the visible and near-infrared spectrum. Six scores are generated for each lesion based on constrained linear classifiers, with each classifier trained to differentiate melanoma from other pigmented lesions (low-grade dysplastic nevus, congenital nevus, common nevus, seborrheic keratosis, solar lentigo, and pigmented basal cell carcinoma). A lesion is then recommended for biopsy if all six scores are above the threshold value. In the first published study by Elbaum et al, results from four clinical centers demonstrated 100% sensitivity and 85% specificity in diagnosing melanoma. More recently, Friedman et al used an imaging database of 990 small pigmented lesions to match a panel of 10 dermatoscopists against MelaFind. They found that while dermatoscopists were able to correctly identify small melanomas with an average sensitivity of 39% and specificity of 82% and recommended small melanomas for biopsy with a sensitivity of 71% and specificity of 49%, MelaFind achieved 98% sensitivity and 44% specificity. MelaFind is not yet commercially available.

**Optical coherence tomography**

OCT uses a fiberoptic Michelson interferometer with a low-coherence length broadband light source, reaching a penetration depth of about 1 mm (depending on the scattering properties of tissue), while lateral resolution is determined by the numeric aperture of the objective. The reflectivity of different tissue components, such as melanin and cell membranes, provides contrast in the images, and the micromorphologic features correlate with histopathologic findings. While the resolution is insufficient to reveal the morphology of single cells, lesion architecture can be evaluated and correlated with surface dermatoscopic parameters (pigment network and brown globules). Gambichler et al examined a panel of melanomas and benign nevi by OCT and found that melanomas showed increased architectural disarray, less defined dermoepidermal borders, and vertically oriented icicle-shaped structures not seen in nevi. While OCT has been used routinely to evaluate ocular lesions, its utility for skin lesions has not been fully established because sensitivity/specitivity studies for melanoma detection have not been reported. OCT appears to be best suited for macular and nonscaling lesions, because histopathologic structures may be less clearly visualized in hyperkeratotic or raised lesions.

**Reflex transmission imaging**

High-resolution B-mode ultrasound has primarily been used in the past to assess the depth/thickness of melanoma tumors. RTI is a form of high-resolution ultrasound that can be used in combination with white light digital photography for classification of pigmented lesions. Rallan et al used RTI to derive sonographic parameters for melanomas and benign pigmented lesions in a group of patients referred by primary care physicians. They found significant quantitative differences to allow discrimination between melanomas, seborrheic keratoses, and nevi to potentially reduce the referral of benign tumors by 65% without missing melanoma. The cost for DermaScan C (2-D mode; Cortex Technology, Hadsund, Denmark) is approximately $50,000 to $60,000. Given the limited reports using RTI in the literature and its high cost, its future utility as a primary imaging modality for melanoma detection is not clear.

**Modalities for detecting new and changing lesions**

**Paradigms for side-by-side comparisons**

The modalities described in the preceding sections are unidimensional, in that they represent
imaging and evaluation of lesions at a single point in time. However, confirmation that a lesion is new or assessment of change in a nevus—both of which are clearly important determinations for early melanoma detection—require observations at multiple points in time. There are currently two paradigms promulgated in the literature to facilitate side-by-side comparisons of nevi for the purpose of documenting changes over time. Both modalities involve comparing previously taken photographs with examinations in real time.

**Serial dermatoscopy and photography**

The first paradigm involves monitoring suspicious nevi for changes over time using serial dermatoscopy and photography. At the initial examination, lesions to be followed are subjected to DELM. The digital photographs are linked to a body map, and DELM images are stored for future visits. At follow-up examinations, the same lesions are rephotographed and serial DELM images are reviewed to assess changes in particular lesions. The generation, archiving, and retrieval of DELM images are usually accomplished using an accessory camera and instrument such as Molemax (3 Gen, LLC), SolarScan (Polartechnics Ltd), or VivaCam (Lucid, Inc; complete systems range from approximately $10,000-$30,000). The major advantage of this approach is the high resolution of DELM, allowing one to observe small changes in lesions over time. Several studies employing MoleMax II found that DELM monitoring was useful for patients with multiple atypical nevi in early melanoma diagnosis and decreased the number of biopsies.\(^{51,52,155}\) Haenssle et al\(^{53}\) monitored 7001 atypical nevi in 530 patients (median follow-up, 32 months), and reported that the chance of success for melanoma detection among lesions suspicious by dermatoscopic criteria increased from 8.3% to 17% when additional DELM-documented changes were present. In addition, one third of the melanomas detected were exclusively identified by DELM-documented changes, indicating that DELM increased the sensitivity of the ELM analysis.\(^{53}\) Short-term DELM monitoring of 318 suspicious melanocytic lesions by Menzies et al\(^{43}\) found that seven of 61 (11%) lesions showing morphologic changes proved to be early melanoma, none of which displayed the classic surface microscopic features of melanoma. In addition, Robinson et al\(^{52}\) reported that DELM monitoring led to increased confidence and comfort with SSE in high-risk patients. Detection of a high fraction of in situ (compared to invasive) melanomas in these studies suggests improved sensitivity for early melanoma detection.\(^{43,51-53}\)

Several pitfalls are intrinsic to this approach. First, only a subset of a patient’s lesions is being monitored in this way, so lesions not imaged (ie, those not deemed clinically atypical at the initial visit) cannot be assessed for changes at follow-up visits. Three studies involving monitoring of high-risk patients found that the majority of nevus-derived melanomas did not develop from clinically atypical nevi.\(^{9,46,54}\)

Such a screening strategy will therefore likely miss melanomas that ultimately arise from benign-appearing nevi. Second, this approach does not allow for detection of new lesions, because only preexisting lesions will have been photographed. Given that at least half of melanomas arise de novo and not from nevi\(^{9,80,83}\) up to 50% of expected melanomas might be missed. Indeed, Kelly et al\(^{9}\) found that 13 of 20 (65%) melanomas in patients with clinically atypical nevi arose as new lesions. Third, while most short-term monitoring studies have revealed observable dermatoscopic changes in growing melanomas,\(^{43-45}\) other longer-term studies found that most dermatoscopic changes in clinically atypical nevi proved to be histologically inconsequential.\(^{54,112}\)

Finally, acquiring, archiving, and retrieving DELM images at each visit is laborious and time consuming,\(^{54}\) and may adversely affect patient compliance for follow-up.\(^{112}\)

**Total body photography**

The second paradigm for achieving side-by-side comparisons involves use of total body cutaneous photography. Clinical regional photographs capturing all existing nevi and “nevus-free” areas of skin are taken using standard poses\(^{156}\) at the initial visit, and these then serve as a baseline for comparison during follow-up examinations. At follow-up examinations, photographs can be used to appreciate new or changing lesions. The focus of this approach is on monitoring for the development of new lesions, with the capacity for detection of changing nevi dependent on the resolution of the photographs. The photographs may be printed and kept in the patient’s chart or electronically archived. We have found MIRROR DermaGraphix software (Canfield Scientific, Fairfield, NJ; approximately $4500 plus $500 annual renewal fee) to be useful for management of the photographs, and its built-in zoom function is helpful for nevus comparisons. High-resolution photographs and zoom capability are also features of the DigitalDerm MoleMapCD (DigitalDerm Inc, Columbia, SC; approximately $300 cost to patient), in which patients are sent to designated photographers, primarily located in Arizona and the southeastern United States, and
CD-ROMs containing the photographs and specialized software are then returned to the physicians.

The effectiveness of total body photography in early melanoma detection and reduction of biopsies in high-risk patients was first demonstrated by Kelly et al.\(^9\) and subsequently in other studies.\(^{21,46,157,158}\) While this approach will easily detect new lesions, it is unlikely to observe small changes in nevi over time, and it is possible that some areas of skin may be covered by undergarments or hair and therefore missed in baseline photographs.

**Combined photographic approach**

Selection of which photographic approach to use may be guided by the type of changes in nevi most likely to occur in a particular patient. For example, in younger patients, it may be problematic to establish a baseline using total body photography if they are expected to develop many new nevi in the short term; dermatoscopic monitoring of particular nevi may be more appropriate if the focus of their surveillance is identifying changes in preexisting lesions over time. On the other hand, total body photography may be more suitable for older patients with fewer nevi, in whom melanoma would be more likely to present as a new rather than changing nevus. It should be noted, however, that use of dermatoscopic or total body photography need not be mutually exclusive. Practitioners may find it useful to incorporate aspects of both modalities. For example, regional photographs may be added for patients in whom DELM images are being monitored. Alternatively, DELM images can be generated for a subset of nevi for closer monitoring in patients undergoing total body photography. Such a combined photographic approach has been advocated in the literature.\(^{53,159}\)

**APPROACH TO THE PATIENT WITH NEVI**

When physicians are confronted with patients with numerous or clinically atypical nevi, there may be a tendency to remove lesions in a prophylactic manner. Such practice of nevus removal may be sought by the patient to reduce their melanoma risk or promulgated by the physician out of fear of missing a melanoma. It is clear that complete removal of a patient’s nevi will not prevent melanoma, which is just as (if not more) likely to arise from isolated epidermal melanocytes anywhere on the skin than from preexisting nevi.\(^{9,80,83}\) However, it is unclear to what extent “molectomy” may reduce long-term melanoma risk in high-risk patients, because to our knowledge this has not been formally studied. Nevertheless, the application of general clinical principles combined with a patient-tailored approach is the best means for achieving the common goals for early melanoma detection (Table I).

An algorithm for the initial evaluation of patients who may be at increased risk for melanoma is depicted in Fig 4. At the initial visit, the patient’s level of risk can be assessed by history and physical examination (see above for risk factors). It is useful to ask if the patient is concerned about any lesions or aware of any that are new or changing. A complete

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**Fig 4.** Algorithm for initial evaluation of patients who may be at increased risk for melanoma.
Management of established patients with nevi

![Algorithm for management of established patients with nevi.](image)

Skin examination may discover lesions suspicious for melanoma. Identification of the signature nevus and its relatives can narrow down the number of lesions that need further examination by dermatoscopy or another imaging modality. Ugly duckling lesions and other lesions about which either the physician or patient is concerned may represent melanoma and should be biopsied or removed. In our recent monitoring study of high-risk patients, we found that many melanomas were diagnosed at the first visit and represented the most clinically atypical lesion. Consequently, it may be useful, particularly in patients who have not previously had many nevi removed, to biopsy such a lesion (if present) at the first visit. Doing so can provide a "histologic baseline" for the patient's most clinically atypical lesion and reassure both the patient and the physician that that lesion is not melanoma. For patients with nevi, one must decide which photographic paradigm or combinatorial approach will be employed for the future assessment of changes. For patients receiving total body photography, lesions in odd locations may be separately photographed, and for isolated lesions a single digital photograph may be sufficient. In addition, one may decide to remove some nevi that are poorly suited for photographic surveillance, such as very dark lesions in which pigmentary changes would be difficult to appreciate over time. Patients should be counseled on sun protection and SSE. The recommended frequency for follow-up visits generally ranges from 6 to 12 months, but should be dictated by the estimated level of patient risk and patient confidence/competence in performing SSE. For patients with numerous or clinically atypical nevi, where one might be concerned about missing a melanoma at the first visit, it can be reassuring to reexamine the patient in 3 to 4 months to confirm that no lesions have undergone photographic changes. Once lesions are confirmed to be stable, longer intervals can be established for follow-up visits.

An algorithm for management of patients with nevi is depicted in Fig 5. At each follow-up visit, the patient should be queried about any new or changing lesions they may have noted on SSE. Such lesions can then be assessed during clinical examination, using baseline photographs to confirm changes and to detect any new or changing lesions. Particular attention should be given to lesions on the back, buttocks, and posterior legs, which are common sites for melanoma and difficult for patients to monitor with SSEs. Indications for biopsy/removal of nevi in this setting are enumerated in Fig 5. These include patient concern (particularly if symptomatic) or
physician concern about a lesion, ugly duckling, photographic confirmation of change (particularly asymmetric changes in previously symmetric or clinically atypical lesions), new lesion that is clinically atypical, and any new lesion in a patient over 50 years of age. Gachon et al. conducted a prospective study to investigate the major principles used by 135 dermatologists to aid in melanoma recognition (and whether a lesion should be excised), and found that most relied on assessment of overall pattern, ugly duckling sign, and knowledge of recent change.

CONCLUSIONS

Although no definitive noninvasive technique is available for diagnosing melanoma, several modalities are now at our disposal to assist the physician in early melanoma detection. Dermatoscopy can increase confidence that a melanocytic lesion is benign or malignant. It is likely that computer-based analysis of dermatoscopic images and multispectral digital dermatoscopy will be increasingly used to increase objectivity and reduce physician to physician variability. While there may be a role for CSLM/RCM, OCT, and RTI in the future, more studies are needed and their availability is limited. Some type of photography is essential for determining whether individual nevi are new or have undergone changes. The limitations of any given modality necessitate a combined approach to maximize success in early melanoma detection. Implementation of a successful melanoma screening program, incorporating SSE, multiple detection modalities, and the general clinical principles outlined in this review should reduce melanoma mortality through earlier detection. A measure of successful implementation would be to have no patients diagnosed with invasive melanoma on a follow-up visit.

REFERENCES


