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NON-INVASIVE DIAGNOSTIC TECHNOLOGIES FOR MELANOMA

Clinical examination followed by excisional biopsy and histopathologic analysis of suspicious pigmented lesions remains the gold-standard for melanoma diagnosis. Unfortunately, the performance of the unaided "melanoma detection pathway" is far from optimal with dermatologists demonstrating only 63.6% sensitivity[1] and primary care physicians only 40.2% sensitivity for correct melanoma identification[2] in a community-based screening setting. The accuracy of unaided melanoma detection is also low with a number needed to excise (NNE), defined as the number of suspicious lesions that must be excised to detect a single melanoma, of 29.4 for non-specialists and 8.7 for specialists.[3] In order to improve melanoma detection, new non-invasive techniques have emerged including dermoscopy, total body photography, reflectance confocal microscopy and the pigmented lesion assay, which have a potential capacity to improve melanoma diagnosis. Such techniques used either alone, in combination, or with computational approaches including artificial intelligence (AI), have the potential to revolutionize the melanoma detection pathway for the benefit of patients and clinicians alike. Some of these technologies also provide an alternative to surgical biopsy in cases where patients decline such a procedure or to aid in the decision of whether to proceed with surgical biopsy when the clinical findings are equivocal. Such techniques also have application in the assessment and monitoring of high-risk patients including those with a history of melanoma, with multiple atypical nevi or with melanoma predisposition syndromes. They may also improve triage of referrals from non-specialists and help reduce healthcare costs by decreasing unnecessary surgical biopsies. In this review, the key features of established and emerging visual and non-visual non-invasive melanoma diagnostic technologies are highlighted.

Visual Techniques: Dermoscopy, Sequential Digital Dermoscopic Imaging and Total Body Photography

Dermoscopy

Of all technological advances aimed at increasing the sensitivity and specificity of melanoma detection, dermoscopy has arguably had the most substantive impact. While the technique dates back more than 100 years, it was not until the publication of a seminal paper by Pehamberger et al. in 1987 that a formalized approach to the interpretation of dermoscopic findings of pigmented lesions, termed "pattern analysis", was established.[4] This study was followed soon after by descriptions of algorithmic approaches to pigmented lesion dermoscopy including the ABCD rule for dermoscopy[5], the 7-point checklist[6], the Menzies rule[7], the CASH

algorithm[8] and the chaos and clues method.[9] In a study comparing the validity and reliability of such criteria when used by dermatologists, general practitioners, medical students and residents, sensitivity for melanoma detection was found to be between 70 and 95%; however, all methods showed poor interobserver agreement.[10] Additionally, many dermatologists likely do not employ any of these algorithms and instead rely on pattern analysis which has been defined as "the simultaneous assessment of the diagnostic value of all dermoscopy features shown by the lesion", an approach which has been shown in one study to have a higher diagnostic accuracy than the ABCD rule and the 7-point checklist.[11] Regardless of the method used for interpretation, there is now an overwhelming body of evidence, including four meta-analyses[12-15], for improvement of melanoma detection through the routine use of dermoscopy.

Sequential Digital Dermoscopic Imaging

Although clinical appearance with the addition of dermoscopy can provide important static information about a pigmented lesion's probability of being classified as melanoma, dermatologists rely on subjective patient history to gain knowledge of dynamic features suggestive of melanoma including lesional change or symptoms. Sequential digital dermoscopic imaging (SDDI) represents a variation of classical dermoscopy which permits objective assessment of lesional evolution. This is accomplished by obtaining baseline digital dermoscopic images and follow-up images and comparing these images for change in size, colour or structure/pattern[16] (**Table 1**). For patients at high-risk for melanoma including those with the familial typical mole and multiple melanoma syndrome or atypical mole syndrome, the use of SDDI has been shown to increase melanoma detection 2-fold compared to the use of the 7-point checklist alone.[17] Additionally, melanomas detected by SDDI are significantly thinner at the time of diagnosis.[17] In low-risk patient groups, however, the addition of SDDI appears to be of limited additional value[18,19] and may in fact lead to false positives.[20] One of the reasons for this, particularly in younger patients, may be that growth represents a normal biologic feature of benign nevi and thus the interpretation of any changes noted with this technique requires careful interpretation to distinguish an expected change of benign nevi from a pathologic feature of melanoma. Features that should prompt excision include (1) architectural changes, (2) asymmetric increase in size, (3) new colors, depigmentation and focal colour changes and (4) the appearance of a melanoma criteria such as black dots or regression (**Table 1**).[21] Limitations of this technique include the possibility of decreased sensitivity if a patient does not return for their follow-up visit, the requirement for digital storage and organization of photos and the additional time required for image comparison. Despite these limitations, SDDI appears to be an effective strategy for improvement in sensitivity as compared to dermoscopy for detecting melanoma which is particularly valuable in high-risk patient populations.

Total Body Photography

Another technique aimed at increasing detection of melanoma in patients with numerous nevi is total body photography (TBP). Advantages of this technique over SDDI are its ability to detect de novo melanomas or melanomas arising within benign appearing nevi not otherwise selected for monitoring.[22] In a study of U.S. academic dermatologists in 2010, 71% of respondents reported regular use of TBP[23]; however, this is likely much lower in the community setting.

In a recent 5-year cohort study of melanoma patients, 48.1% of second primary melanomas were detected using TBP with a number needed to excise of 1:1.3.[24] It has also been associated with a reduction in biopsies and a lower NNE[25,26] in some studies but no difference in biopsy rates in others.[27] Part of the reason for such discrepancies might be the rapidly changing technology available to both acquire and interpret TBP images with the most advancements being automated and 3-dimensional TBP.[27] Limitations of this technique include the significant cost of equipment, the

Interval Change	Nevus	Melanoma
Size	No growth Symmetrical growth	Asymmetric growth
Colour	No change Even lighter/darker brown Even lighter/darker erythema	New colours, especially focally Depigmentation
Structure	No change Subtle changes including accentuation of existing structures	Architectural changes Appearance of new structures including classical melanoma criteria and regression

Table 1. *Differentiating features of nevus and melanoma in follow-up images (Adapted from Tschandl et al.)[21]*

need for a dedicated space and personnel, and the time required for image acquisition and analysis. An added benefit of TBP is the decrease in cancer worry.[28]

Non-Visual Techniques: Reflectance Confocal Microscopy and Pigmented Lesion Assay

Reflectance Confocal Microscopy

Reflectance confocal microscopy (RCM) is a technique which allows for imaging to a depth of the upper papillary dermis (a depth of 200 µm) with a near-infrared laser (830 nm).[29] In a recent meta-analysis, RCM was found to have a pooled sensitivity of 92.7% and specificity of 78.3% for melanoma detection.[29] Additionally, in a prospective study of RCM in combination with dermoscopy, the addition of RCM decreased the NNE from 14.6 to 6.8.[30] When compared to dermoscopy, it is superior for recognition of in situ melanoma and diagnosis of amelanotic lesions and mucosal lesions; however, it cannot be used on acral skin.[29] Its widespread use is also limited by the significant cost of purchase and maintenance as well as the substantial training required to gain proficiency.

Pigmented Lesion Assay

The pigmented lesion assay (PLA) is a proprietary test developed by DermTech, Inc. (La Jolla, CA) which is designed to aid in deciding whether to proceed with surgical biopsy of pigmented lesions. Its use involves harvesting cells from the stratum corneum overlying a pigmented lesion in question using a non-invasive "tape stripping" method, followed by the measurement of transcript levels of two genes that are expressed predominantly by melanoma as compared to benign pigmented lesions (LINC00518 and PRAME). While the validation and registry studies for the PLA showed a 91-95% sensitivity and 53-91% specificity for melanoma detection with an estimated negative predictive value (NPV) of 99%[31,32], several follow-up analyses have been critical of the prevalence rates used to calculate this NPV and propose less impressive performance metrics in the real-world setting.[10,33] Further studies are required to establish the role of the PLA in the melanoma detection

Technology	Description	Advantages	Cost	Disadvantages and Limitations
Dermoscopy	Direct examination of pigmented lesions with polarized/non-polarized magnification	Well-validated Efficient and convenient for both patient and provider	$	Requires significant training/experience to gain proficiency Time consuming if many lesions
SDDI	Longitudinal dermosocpic re-imaging of individual lesions	Good evidence for increasing melanoma detection in high-risk populations Minimal additional equipment required	$$	Limited by patient compliance Lengthy time for acquisition/ comparison Digital storage required
TBP	Clinical imaging of entire skin surface Automated TBP machines available from Canfield Scientific (Parsippany, NJ), DermSpectra (Tucson, AZ), Fotofinder (Columbia, MD) and Melanoscan (Stamford, CT)	Allows for identification of new and changing lesions Image acquisition does not need to be done by dermatologist	$$$	Most units require dedicated space Referencing TBP images may lengthen time of office visit
RCM	In vivo near histology-grade imaging to level of papillary dermis	Can be used on amelanotic, facial or mucosal lesions Helpful for presurgical mapping	$$$	Image capture takes up to 5 minutes per lesion Cannot be used on acral skin Significant training/ experience required for image interpretation
PLA	Diagnostic test involving "tape stripping" followed by measurement of LINC00518 and PRAME	Rapid procedure (<5 min) Useful for cosmetically sensitive areas or as alternative for patients that decline surgical biopsy Rapid turnaround time High negative predictive value	$$	Controversy remains whether sensitivity and specificity are sufficiently high Cannot be used on acral or mucosal surfaces

Table 2. *Comparisons of non-invasive melanoma diagnostic technologies (Adapted from Fried et al.[34,35])*
SDDI, serial digital dermoscopic imaging; TBP, total body photography; RCM, reflectance confocal microscopy; PLA, pigmented lesion assay

pathway; nevertheless, it provides a promising proof-of-concept for in vivo molecular diagnostics for melanoma.

Conclusion and Future Directions

Melanoma remains a challenge for even the most experienced dermatologist with significant clinical consequences for a delayed or missed diagnosis. As clinicians, we must be judicious with the employment of any new diagnostic technique, particularly those that carry significant financial costs or potential for harm, but also open to their use if they can improve diagnostic accuracy thereby leading to earlier detection and treatment. The non-invasive techniques described herein, along with new and emerging techniques including high-frequency ultrasound, optical coherence tomography and electric impedance spectroscopy, have the potential to improve the efficiency and efficacy of the melanoma detection pathway for the benefit of both dermatologists and their patients (**Table 2**). Nonetheless, clinicians must remain vigilant of "technological creep" and only adopt such techniques when there is ample comfort with their evidence and risk-benefit ratio.

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