Visual Assessment and Dermoscopy Enhanced By Non-invasive Genomic Testing

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Introduction and Objective

Early detection of melanoma is critical to optimizing patient outcomes.[1] Dermoscopy supports visual inspection of pigmented lesions that raise concern for melanoma,[2] and generally improves overall accuracy when ruling out melanoma.[3] Numerous dermoscopic findings have been proposed as sensitive and specific features of melanoma, and various combinations of them have been used to generate checklists and algorithms to aid in biopsy decision-making.[2] However, since melanoma-specific dermoscopic criteria are complex and have primarily been studied within invasive melanomas, they may be less reliable for *in situ* melanoma.[4-6] In addition, the performance of dermoscopy is influenced by the training and experience of the user.[2] For these reasons, alternative approaches to pigmented lesion assessment continue to be of interest.

Non-invasive assessment of melanoma-associated genomic biomarkers has been shown to be effective in ruling out melanoma in uncertain pigmented skin lesions with a sensitivity of 91-97%, specificity of 53-69%, and negative predictive value ≥99%.[7,8] RNA gene expression of Preferentially Expressed Antigen in Melanoma (PRAME) and Long Intergenic Non-Coding RNA 518 (LINC), along with somatic DNA mutations in Telomerase Reverse Transcriptase (TERT), are detected in samples of stratum corneum overlying pigmented lesions collected non-invasively using adhesive patches.[7]

The objective of this retrospective case series analysis was to determine whether non-invasive assessment of genomic biomarkers could enhance visual and dermoscopic detection of pigmented lesions at risk for melanoma.

Methods

The EMR of a large dermatology practice was queried for all melanomas diagnosed during a one-year period, which revealed 59 cutaneous melanomas, All 59 had undergone non-invasive genomic assessment,[7,9] and a checklist-guided dermoscopic exam performed by a dermatologist highly experienced in dermoscopy prior to biopsy (G.P., confirmed by M.K.S.).

Clinical and dermoscopic images were available for all lesions, each of which was reviewed for 5 clinical and 13 dermoscopic features (Table 1).[10]

Table 1. Clinical and Dermoscopic features

Clinical features	Asymmetry, border irregularity, color variability (black pigment was assessed separately), and diameter ≥6 mm.
Dermoscopic features	Absent or diminished pigment network, regression structures, granularity (peppering), globular disorganized pigment network, reticular disorganized pigment network, homogeneous disorganized pigment network, radial streaming, network thickening at the periphery, focal pseudopods, vascular changes (twisted, dotted), negative pigment network, shiny white lines, and blue-grey-white veil.

Methods (cont.)

Non-invasive genomic analysis was conducted using adhesive patches (DermTech, Inc., La Jolla, CA) to collect tissue from the stratum corneum of all 59 melanomas. Nucleic acids extracted from the tissue samples were assessed for PRAME and LINC RNA, and in cases with sufficient material, DNA was sequenced to detect mutations in the TERT promoter region. Gene expressions of PRAME and LINC were quantified by qPCR, and TERT DNA mutations were assessed by Sanger sequencing.[13,15] Histopathologic diagnoses were established by routine light microscopy (supplemented in many cases by immunohistochemistry) and confirmed by consensus discussions with dermatopathologists at two university tumor boards.

Results

Of 59 melanomas, 42 (71.1%) were *in situ* and 17 (28.8%) were invasive melanoma. All melanomas were positive for 1 or more melanoma-associated genomic markers. *In situ* lesions had an average of 3.48 (range 0-7) dermoscopic features while invasive melanomas had an average of 4.71 (range 2-7) (p=0.05). Half of the 42 *in situ* melanomas (n=21, 50%) and 3 of 17 (18%) invasive melanomas had 3 or fewer dermoscopic features (Figure 1).
When combining dermoscopic and clinical features, the average number of features for *in situ* lesions was 6.29 (range 1-9) compared to invasive lesions with 8.18 features (range 4-11, p=0.02).

Figure 1. Number of dermoscopic features for *in situ* and invasive melanomas.

	In situ N=42		Invasive N=17	
Dermoscopic Features	n	%	n	%
0	3	7%	0	0%
1	0	0%	0	0%
2	4	10%	1	6%
3	14	33%	2	12%
4	13	31%	5	29%
5	5	12%	4	24%
6	2	5%	3	18%
7	1	2%	2	12%

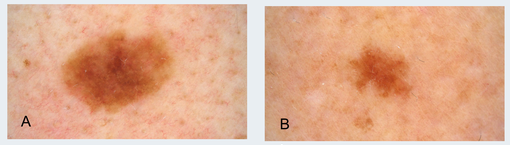
By non-invasive genomic assessment, 29 lesions (49.2%) expressed 2 genomic markers, 28 (47.5%) expressed PRAME and LINC and 1 lesion (1.7%) expressed PRAME and TERT. Twenty-eight lesions (47.5%) expressed 1 marker, 19 (32.2%) expressed LINC only, 7 (11.9%) expressed PRAME only, and 2 (3.4%) expressed TERT only. Two lesions (3.4%) expressed all 3 markers (LINC, PRAME, and TERT).

The most common genomic marker detected was LINC (n=50, 84.7%) followed by PRAME (n=39, 66.0%). Figure 1 depicts examples of assessed cases of *in situ* melanomas with few or subtle dermoscopic features and the genomic markers present in the lesions.

Results (cont.)

Figure 1. Examples of *in situ* melanomas with minimal features (genomic markers present)

A. *In situ,* minimal dermoscopic features (LINC and PRAME)
B. *In situ,* minimal dermoscopic features (PRAME)



Conclusion

Evaluating pigmented lesions to rule out melanoma and appropriately guide biopsy decisions remains challenging, even for experienced dermoscopists.[12,13] Earlier *in situ* and some invasive melanomas can have few or minimal morphologic features on visual and dermoscopic inspection.[5,6] Non-invasive genomic testing may enhance biopsy decision making in this situation.[7-9,11]

References

1. Petrie T, Samatham R, Witkowski AM, Esteva A, Leachman SA. Melanoma early detection: big data, bigger picture. *J Invest Dermatol.* 2019;139(1):25-30.
2. Dinnes J, Deeks JJ, Chuchu N, et al. Dermoscopy, with and without visual inspection, for diagnosing melanoma in adults. *Cochrane Database Sys Rev.* 2018;12(12):Cd011902.
3. Wolner ZJ, Yelamos O, Liopyris K, Rogers T, Marchetti MA, Marghoob AA. Enhancing skin cancer diagnosis with dermoscopy. *Dermatol Clin*. 2017;35(4);417-437.
4. Argenziano G, Kittler H, Ferrara G, et al. Slow-growing melanoma: a dermoscopy follow-up study. *Br J Dermatol.* 2010;162(2):267-273.
5. Lallas A, Longo C, Manfredini M, et al. Accuracy of dermoscopic criteria for the diagnosis of melanoma in situ. *JAMA Dermatol.* 2018;154(4):414-419.
6. Rose SE, Argenziano G, Marghoob AA. Melanomas difficult to diagnose via dermoscopy. *G Ital Dermatol Venereol.* 2010;145(1):111-126.
7. Gerami P, Yao Z, Polsky D, et al. Development and validation of noninvasive 2-gene molecule assay for cutaneous melanoma. *J Am Acad Dermatol.* 2017;76(1):114-120.e112.
8. Skelsey MK, Rock J, Howell MD, et al. Non-invasive detection of genomic atypia increases real-world NPV and PPV of the melanoma diagnostic pathway and reduces biopsy burden. *Skin.* 2021;5(5):512-523.
9. Jackson SR, Jansen, B, Yao Z, et al. Risk stratification of severely dysplastic nevi by non-invasively obtained gene expression and mutation analysis. *Skin.* 2020;4(2):105-110.
10. Markowitz O. *A Practical Guide to Dermoscopy.* Wolters Kluwer; 2017:9-23.
11. Ferris LK, Jansen B, Ho J, et al. Utility of a noninvasive 2-gene molecular assay for cutaneous melanoma and effect of the decision to biopsy. *JAMA Dermatol.* 2017;153(7):672-680.
12. Ianosi SL, Calbureanu-Popescu MX, Ianosi NG, et al. The importance of dermoscopy in early recognition of melanoma in situ. *Curr Health Sci J.* 2019;45(4):366-371.
13. Petty AJ, Ackerson B, Garza R, et al. Meta-analysis of number needed to treat diagnosis of melanoma by clinical setting. *J Am Acad Dermatol.* 2020;82(5):1158-1165.

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