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Genomic Analysis Aids in the Management of Dermoscopically Atypical Pigmented Lesions

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ABSTRACT

Background: Numerous melanoma-specific dermoscopic features have been described in invasive melanomas, while fewer features are found in melanoma in situ (MIS) and atypical nevi (ATN). Consensus regarding which features are critical for the differentiation of MIS from ATN has not been reached.

Purpose: Determine 1) whether there are dermoscopic features that differentiate early MIS from ATN, and 2) whether non-invasive assessment of genomic biomarkers (LINC00518 and PRAME) can aid in patient management.

Methods: From 2018 to 2023, 56 melanomas were evaluated for 5 clinical and 13 dermoscopic features and melanoma-associated genomic biomarkers. Two groups of ATN with positive and negative genomic biomarkers were randomly selected for comparison.

Results: All melanomas in this study expressed one or both melanoma-associated genomic markers. MIS had an average of 3.90 (range, 2–7) of the 13 dermoscopic features, while invasive melanomas had an average of 4.44 (range, 3–6). Sixteen of 40 (40%) MIS and 3 of 16 (18.8%) invasive melanomas had 3 or fewer dermoscopic features. These findings were comparable to those observed in both ATN groups. The most common dermoscopic features were absent or diminished pigment network, regression structures, and granularity. This combination of features was most helpful in identifying lesions for genomic testing.

Conclusions: Clinical and dermoscopic features alone could not differentiate MIS from ATN. Non-invasive genomic testing helped differentiate lower from higher-risk lesions and aid in clinical management decisions. Genomic testing was particularly helpful in patients with large numbers of lesions with several being considered for biopsy based on clinical and dermoscopic examination.

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INTRODUCTION

Early detection of melanoma is critical to optimizing patient outcomes.[1] Dermoscopy aids in the evaluation of equivocal pigmented lesions that are suspicious for melanoma.[2,3] However, the most well-known melanoma-aligned dermoscopic features have primarily been described within invasive melanomas. These criteria may not be found in melanoma in situ,[4-6] making it difficult to differentiate them from atypical nevi (ATN).[7,8] In addition, the performance of dermoscopy is influenced by the training and experience of the user.[2] Therefore, the use of objective, non-invasive genomic assessment may improve the biopsy decision-making process.

Dermoscopy, also known as dermatoscopy or epiluminescence microscopy, allows for the magnified, illuminated inspection of skin lesions unobstructed by surface reflections.[3] It is increasingly used to help rule out melanoma and support biopsy decisions for clinically uncertain or ambiguous pigmented skin lesions. Dermoscopy is widely used by dermatologists but only minimally by primary care providers and other clinicians performing biopsies.[9] Multiple meta-analyses found that dermoscopy increases sensitivity over visual assessment alone, but its accuracy is highly experience-dependent.[2,10,11] Ferris and colleagues reported a sensitivity of 71% and specificity of 59% for experienced dermatologists using dermoscopy to evaluate pigmented lesions for melanoma[12] but noted that accuracy calculations for dermoscopy are complicated by its inherent subjectivity and other variables such as the experience of the user.

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] Yet consensus is lacking, even among experts, as to which specific features, checklists, and algorithms should be adopted or considered "standard" for in situ melanomas and for thin invasive melanomas.[2] Several investigations have concluded that the dermoscopic features of in situ melanoma may differ and be fewer in number by comparison to invasive melanomas and that interobserver concordance may be lower.[5,13] These limitations affect all users of dermoscopy but may be particularly relevant to primary care providers and other non-dermatologists.[7,14] For these reasons, additional approaches to pigmented lesion assessment continue to be of interest. Objective methods, largely independent of training or experience, and that are particularly suitable for lesions with minimal or subtle visual and/or dermoscopic features appear especially attractive.

Recently, non-invasive assessment of melanoma-associated genomic biomarkers has been shown to be an effective aid in deciding to biopsy equivocal pigmented skin lesions. RNA gene expression of Preferentially Expressed Antigen in Melanoma (PRAME) and Long Intergenic Non-Coding RNA 518 (LINC00518) can be detected non-invasively in samples of stratum corneum overlying pigmented lesions that are collected using adhesive patches.[15,16] The sensitivity and specificity of these genomic markers for melanoma are 91% and 69%, respectively.[16] In real-world, intended-use populations, the non-invasive genomic patch testing has a negative predictive value (NPV) of ≥99% and a positive predictive value (PPV) of 18.7% for melanoma.[17] While intended to help rule out melanoma and not to definitively distinguish melanoma from ATN, analyses of these non-invasively obtained genomic markers may supplement visual and dermoscopic examinations to guide biopsy decisions in an objective manner, particularly for lesions with few or equivocal morphologic features.[16,17]

The purpose of this cohort study was to determine whether 1) there are reliable dermoscopic features to differentiate the earliest forms of in situ melanoma from ATN, and 2) whether non-invasive assessment of genomic biomarkers (LINC00518 and PRAME) can enhance visual and dermoscopic evaluation and patient management.

MATERIALS AND METHODS

In our large US dermatology practice focused on pigmented lesion management, total body skin examinations, photography, dermoscopy, and genomic assessments are routinely used to help determine which of several atypical lesions require biopsy. In this cohort study of cases collected within DermTech (DermTech, Inc., San Diego, CA) patient registries (WCG, Princeton, NJ), electronic medical records (EMR) (July 26, 2018 – March 16, 2023) from our practice were used to identify all the melanomas diagnosed in the study time frame for which 5 clinical and 13 dermoscopic features (Table 1), as well as genomic assessments (DermTech Melanoma Test, DMT, DermTech, Inc., San Diego, CA) were used to rule out melanoma.[16,18-20] Two similarly sized ATN groups (including ATN negative and ATN positive for LINC00518 and/or PRAME from the same time frame) were also assessed using 5 clinical and 13 dermoscopic features that were randomly selected to enable comparisons. The mean number of clinical and dermoscopic features was tabulated for each lesion, and differences between both groups of ATN (genomic assessment negative and positive), in situ melanoma, and invasive melanomas were assessed and compared. Formal statistical analyses of subjectively assessed clinical and dermoscopic features were avoided following expert advice (Michael Walker PhD). Histopathologic diagnoses were established by routine light microscopy (hematoxylin and eosin-stained slides supplemented by immunohistochemistry as needed) and confirmed by consensus discussions with dermatopathologists at two university tumor boards.

RESULTS

Cohort Characteristics

Fifty-six melanomas were identified in the study time frame, all of which expressed at least one melanoma-associated genomic biomarker (LINC00518 and/or PRAME). Of the randomly selected ATN with appropriate high-quality images, 35 were genomically positive and 34 were genomically negative. While similarly sized comparator groups were selected to facilitate the assessment of dermoscopic features, it is important to ascertain that approximately 91% of genomically assessed concerning lesions test negative for LINC00518 and/or PRAME. For the melanoma cohort, the average age at diagnosis was 64.3 years, and 36 (64.3%) were male (Table 2). Additional demographic and lesion location details are summarized in Table 2.

TABLE 1.

Clinical and Dermoscopic Features Examined		
Asymmetry Border irregularity Color variability Diameter >6 mm Black pigment	Absent or diminished pigment network Regression structures Granularity (peppering, annular granular, linear granular, irregular dots and globules) Globular network Reticular network Homogeneous network	Radial streaming Network thickening at the periphery Focal pseudopods Vascular changes (twisted, dotted) Negative pigment network Shiny white lines Blue-white veil

TABLE 2.

Cohort Characteristics					
Cohort	% Male	Age Mean (SD)	Age median (Range)	Number of lesions	Lesion location n(%)
Melanoma	64.3	64.3 (15.2)	64 (24-100)	56	13 (23.6) Head & Neck 27 (49.1) Torso 15 (27.3) Extremities
ATN with positive genomic assessment	37.1	53.4 (16.3)	56 (12-80)	35	3 (8.6) Head & Neck 24 (68.6) Torso 8 (22.8) Extremities
ATN with negative genomic assessment	23.5	53.6 (17.5)	58.5 (22-90)	34	4 (11.8) Head & Neck 25 (73.8) Torso 5 (14.7) Extremities

Lesions: Melanomas and ATN

Of the 56 melanomas, 40 (71.4%) were in situ and 16 (28.6%) were invasive. Fourteen of the 16 (87.5%) invasive melanomas had a mean depth of 0.4 mm (range, 0.2–0.6 mm). The 15th had a depth of 1.0 mm, and the 16th had a depth of 1.5 mm. All melanomas had detectable levels of LINC00518 and/or PRAME gene expression. No discordant and potentially false negative melanomas (gene expression negative cases histopathologically diagnosed as in situ or invasive melanomas) were identified within this study. There were no deeply invasive tumors in this group which could affect the types of dermoscopic features observed.

All the ATN with positive genomic assessments were subsequently biopsied and read by histopathology as benign or mildly dysplastic nevi (n=21, 60%), moderately dysplastic nevi (n=9, 25.7%), and severely dysplastic nevi (n=5, 14.3%). One of the ATN with a negative genomic assessment was biopsied the day of the testing, one was biopsied eight months after the negative genomic testing, and another 18 months after. All were read as benign compound nevi or junctional nevi by histopathology. The other 31 ATN with negative genomic tests were monitored over an average of 25 months (range, 20–29 months) and showed no signs of change warranting biopsy. Three were retested for LINC00518 and PRAME gene expression during this monitoring period and remained negative.

Clinical Features

The number and type of clinical features identified in each group are outlined in Table 3. Although some of the clinical features were seen more often in the melanoma groups, there is a clear overlap between groups in this cohort study. The in situ melanomas are split into 2 groups (3 or fewer dermoscopic features and 4 or more dermoscopic features) to examine whether the clinical features might help to differentiate the in situ melanomas with fewer dermoscopic features from the ATN. Table 3 shows that in situ melanomas had a higher rate of asymmetry compared with the ATN (56.3% vs 25.7-32%), but clinical features were overall not suitable to adequately differentiate them.

Dermoscopic Features

In situ melanomas had an average of 4.00 (range, 2–7) dermoscopic features, while invasive melanomas had an average of 4.28 (range, 3–6), indicating there was not a clear difference in the average number of features between the in situ and invasive melanoma groups (Table 4). However, it is important to note that 16 of the 40 (40%) in situ melanomas and 3 of the 16 (18.8%) invasive melanomas had 3 or fewer dermoscopic features, which overlapped with the ATN groups (Figure 1).

The ATN with negative genomic assessments had an average of 2.26 (range, 1–4) dermoscopic features and the ATN with positive

TABLE 3.

Clinical Features Observed					
Clinical features	ATN negative genomic assessment (n=34) n (%)	ATN positive genomic assessment (n=35) n (%)	In situ melanomas with 3 or fewer dermoscopic features (n=16/40, 40%) n (%)	In situ melanomas with 4 or more dermoscopic features (n=24/40, 60%) n (%)	Invasive melanomas (n=16) n (%)
Asymmetry	11 (32)	9 (25.7)	9 (56.3)	15 (62.5)	13 (81)
Border irregularity	15 (44.1)	7 (20.0)	7 (43.8)	14 (58.3)	6 (37.5)
Color variability	16 (47.1)	16 (45.7)	6 (37.5)	10 (41.7)	10 (62.5)
Diameter >6 mm	18 (52.9)	16 (45.7)	9 (56.3)	20 (83.3)	11 (68.8)
Black pigment	5 (14.7)	9 (25.7)	5 (31.3)	7 (29.2)	10 (62.5)

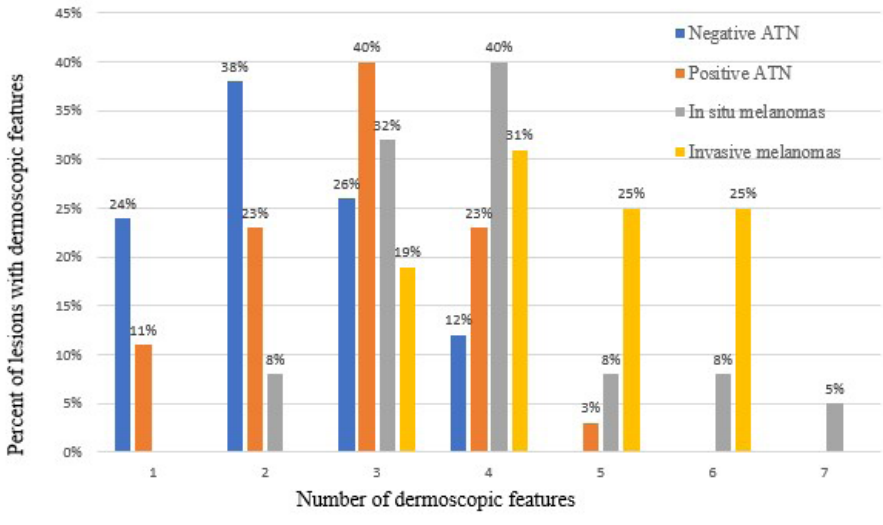
genomic assessments had 2.83 (range, 1–5). Lesions with only one or two dermoscopic features were most commonly PLA-negative ATN. Lesions with 5 to 7 dermoscopic features were the most commonly invasive melanomas. However, 13 of the 34 negative ATN (38%) and 22 of the 35 positive ATN (62.9%) had three or four dermoscopic features, further illustrating the overlap between ATN and melanomas (Figure 1).

Table 4 compares the number and type of dermoscopic features observed among ATN that tested negative for genomic

TABLE 4.

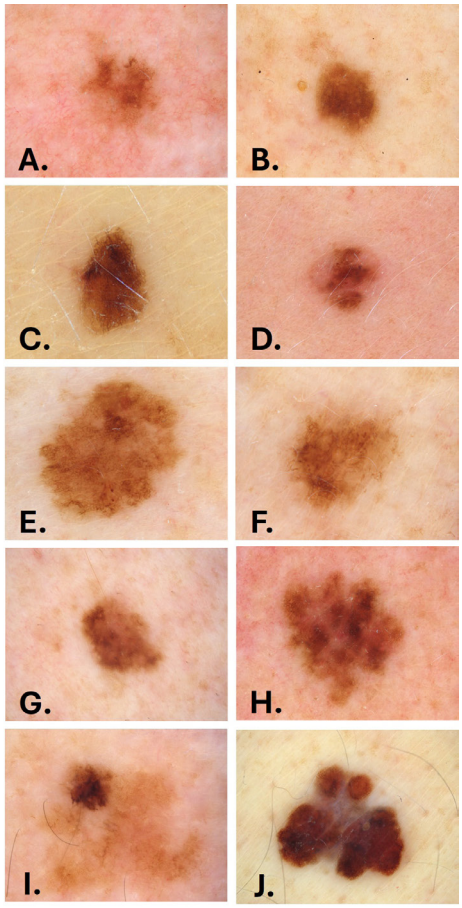
Dermoscopic Features Observed					
Dermoscopic features	ATN negative genomic assessment (n=34) n (%)	ATN positive genomic assessment (n=35) n (%)	In situ melanomas with 3 or fewer dermoscopic features (n=16/40, 40%) n (%)	In situ melanomas with 4 or greater dermoscopic features (n=24/40, 60%) n (%)	Invasive melanomas (n=16) n (%)
Absent (A) or diminished pigment network	27 (79.4)	27 (77.1)	15 (93.8)	24 (100)	16 (100)
Regression (R) structures; white scarring; circular or oval; often reddish in color	20 (58.8)	20 (57.1)	13 (81.3)	24 (100)	16 (100)
Granularity (G): annular, linear, peppering, irregular dots and globules	11 (32.4)	18 (51.4)	14 (87.5)	22 (91.7)	16 (100)
Vascular changes (twisted, dotted)	6 (17.6)	9 (25.7)	0	19 (79.2)	10 (62.5)
Reticular disorganized pigment network	9 (26.5)	4 (11.4)	1 (6.25)	9 (37.5)	0
Globular disorganized pigment network	0	8 (22.9)	0	1 (4.2)	0
Homogeneous disorganized pigment network	0	0	0	1 (4.2)	3 (18.8)
Radial streaming	0	3 (8.6)	0	2 (8.3)	2 (12.5)
Network thickening at periphery	4 (11.8)	6 (17.1)	2 (12.5)	6 (25)	2 (12.5)
Focal pseudopods	0	0	0	0	2 (12.5)
Negative pigment network	0	3 (8.6)	0	0	0
Shiny white lines	0	0	0	3 (12.5)	2 (12.5)
Blue-white veil	0	0	0	0	3 (18.8)

FIGURE 1. Proportion of lesions by number of dermoscopic features observed.



markers, ATN that tested positive for genomic markers, in situ melanomas, and invasive melanomas with a focus on the 3 most common dermoscopic features: absent or diminished pigment network, regression structures, and granularity (the "ARG Criteria or the "ARG Algorithm"). Additionally, the in situ melanomas were divided into groups with 3 or fewer dermoscopic features and those with 4 or more to analyze which features were found most often in the melanomas with fewer features. The table demonstrates that the in situ melanomas with few morphologic features on dermoscopic inspection had overlapping features with the ATN group. Therefore, their dermoscopic features did not reliably differentiate them from the ATN. Three of the invasive melanomas also had only three dermoscopic features, all of which overlapped with the ATN (ie, ARG Criteria).

FIGURE 2. Dermoscopic images of ATN (genetic expression negative), ATN (genetic expression positive), in situ melanomas, and invasive melanomas with variable dermoscopic features and gene expressions. (A) Atypical nevus negative (LINC00518-, PRAME -), (B) Atypical nevus negative (LINC00518-, PRAME-), (C) Atypical nevus positive (LINC00518+, PRAME-), (D) Atypical nevus positive (LINC00518+, PRAME+), (E) In situ with minimal dermoscopic features (LINC00518+, PRAME+), (F) In situ with minimal dermoscopic features (LINC00518-, PRAME+), (G) In situ with typical dermoscopic features (LINC00518+, PRAME+), (H) In situ with typical dermoscopic features (LINC00518+, PRAME+), (I) Invasive melanoma with typical dermoscopic features (LINC00518+, PRAME-), (J) Invasive melanoma with typical dermoscopic features (LINC00518+, PRAME+).



Genomic Assessments

By non-invasive genomic assessment, all the melanomas expressed at least one biomarker. Twenty-eight melanomas (50%) expressed both genomic markers (LINC00518 and PRAME), 19 (33.9%) expressed LINC00518 only, and 9 (16.1%) expressed PRAME only. Four of the 35 (11.4%) ATN with positive genomic assessments expressed both genomic markers, 21 (60%) expressed LINC00518 only, and 10 (28.6%) expressed PRAME only.

Figure 2 depicts representative examples of dermoscopic photos from assessed cases (ATN with positive and negative genomic assessments, in situ melanomas and invasive melanomas) with 3 or fewer dermoscopic features as well as representative cases with 4 or more features. Those with few or subtle dermoscopic features were often featureless on visual examination. Their non-invasively assessed gene expression results are also noted.

DISCUSSION

Identifying melanoma early is critical to optimizing patient outcomes.[1] However, determining which atypically appearing pigmented lesions warrant biopsy and histopathologic examination can be challenging. It is established that early-stage melanomas may exhibit either a paucity of morphological features or their features overlap with both genomic assessment negative and positive ATN. Moreover, dermoscopic interpretation is highly subjective.[5,6] By providing objective data that complements visual and dermoscopic assessment, non-invasive genomic testing may improve care by aiding in the decision as to which lesions to biopsy, particularly in patients with numerous atypical appearing nevi.[21]

In this cohort study, fewer dermoscopic features were detected among in situ melanomas compared to those that were invasive. Overall, 40% of in situ and 18.8% of invasive melanomas presented with 3 or fewer dermoscopic features, and most importantly, the dermoscopic features could not reliably differentiate the earliest stages of in situ melanomas from the ATN (Table 4). As noted, interpretation of dermoscopic features is experience-dependent, and lesions with fewer common features may make assessment difficult for inexperienced dermoscopists.[4-6,13] Ramji and colleagues (2021) found that the probability of an in situ melanoma displaying ≥3 dermoscopic features correlated with time, indicating that earlier lesions were likely to have the fewest features.[13]

A lack of consensus regarding which dermoscopic features should be expected in early melanoma lesions adds further complexity. Key dermoscopic criteria described here and

elsewhere[22-25] that we refer to as "ARG Criteria" (absent or diminished pigment network, regression structures, and granularity), are the most useful, yet not sufficient, features to identify lesions of concern that benefit from additional assessment and efforts to rule out melanoma more reliably. Granularity, in particular, has been considered the dermoscopic feature most closely associated with the identification of early melanoma.[22] In addition to ARG, abnormal vascular features, such as dotted vessels, are helpful for melanoma identification. Vascular changes were more frequently seen in addition to the ARG features in this cohort but were not found in the in situ melanomas with few features. Dotted vessels were more readily observed in areas of regression when dermoscopic photos were enlarged and viewed on a computer monitor, but most clinicians are making management decisions without the benefit of computer visualization. Other researchers have tried to identify the optimal dermoscopic criteria for early melanoma but still lack agreement. Argenziano and colleagues (2010) concluded that asymmetrical pigmentation, reticular overall pattern, and regression were the most frequent dermoscopic characteristics of melanoma in situ.[4] More recently, Lalla and colleagues (2018) found that irregular hyperpigmented areas and prominent skin markings were most common in melanoma in situ.[5] Ianosi and colleagues (2019) identified atypical pigment network, blue-whitish veil, and atypical vascular patterns as the most relevant criteria for melanoma in situ.[26] Since consensus is lacking, even among experts, the risk of missing early melanomas remains a concern. Clinical decisions based on limited or conflicting information may result in a lower threshold for biopsy, since clinicians striving to minimize the risk of missing melanoma may do so at the expense of lower specificity.

The ability to distinguish benign lesions from melanomas is often measured by the number needed to biopsy (NNB), which is the proportion of pigmented lesion biopsies that are diagnosed as melanoma by histopathology.[27] Within the many published reports, the NNB ranges from 6 to over 40 and is thought to be influenced by clinician expertise and clinical settings.[27,28] In this cohort study, all the melanomas diagnosed in the study time frame expressed one or both melanoma-associated genomic markers (ie, LINC00518 and/or PRAME), including those with fewer visual or dermoscopic features. The groups of LINC00518- and/or PRAME-negative and -positive ATN were randomly selected to establish comparator cohorts. Many of the visual and dermoscopic features overlapped between the melanomas and ATN and did not reliably differentiate them from melanoma in situ.

In our clinic, we find it essential to use genomic testing to aid in the decision to biopsy which, if any, of often several clinically atypical lesions present on a given patient. Recent unpublished analyses of approximately 500 lesions entered into a registry from this clinical practice indicated that 86% of lesions that had undergone non-invasive genomic assessments tested negative. Lesions with positive genomic assessments were biopsied and fell into the following histopathologic categories: melanoma (25.8%), dysplastic nevi (43.9% [10.6% mild, 16.7% moderate, 16.7% severe]), and non-melanocytic (15.2%). Based on recent quality control reviews, adequate RNA is collected for successful analysis more than 94% of the time.

This also supports the findings by Ferris et al that genomic testing can be an additional tool to help inform appropriate biopsy decisions and decrease the NNB.[21] The non-invasive genomic test employed, if negative, helps to rule out melanoma with a 99% negative predictive value. If positive, it supports clinicians with a positive predictive value of 18.7% as established previously.[17]

These findings create the foundation for future prospective studies to ascertain how dermoscopy and other visual and morphology-based assessment methods correlate with genomic assessment. They also confirm that a substantial proportion of in situ melanomas may be difficult to rule out by morphology alone because their features are subtle, overlapping, and/or few. Non-invasive assessment of genomic markers appears well suited to complement clinical assessment including dermoscopy to improve biopsy decision-making and pigmented lesion management.[16,17,21]

CONCLUSION

Evaluating pigmented lesions to rule out melanoma and appropriately guide biopsy decisions remains challenging, even for experienced dermoscopists.[26,27] Earlier in situ and some invasive melanomas can have few or minimal morphologic features on visual and dermoscopic inspection[5,6] as seen in this cohort study. Therefore, dermoscopic features, although important, may not reliably differentiate the earliest stages of in situ melanoma from ATN. Non-invasive genomic testing provided an additional technology that helped in guiding the decision as to which of many concerning pigmented lesions to biopsy and which to monitor, as previously demonstrated,[16,17,21] thereby enabling superior pigmented lesion management.

Limitations

Limitations of this study include small cohort size, subjectivity of the clinical and dermoscopic assessment of the melanocytic lesions, and the study's single site setting.

DISCLOSURES

GLP and MKS are clinical investigators and consultants for DermTech; BJ and LEC are employees of DermTech. SWM is a former employee of DermTech. SRJ and RAR have no conflicts of interest.

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