A Retrospective Review: Our Experience With an Adhesive-Based Pigmented Lesion Assay Used to Evaluate Cutaneous Lesions Suspicious for Melanoma

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Background: Being one of the largest dermatology groups in the country with an in-house pathology laboratory, we have seen a significant increase in the number of adhesive-based pigmented lesion assays (ABPLAs) in addition to biopsies and excisions following a moderate-risk or high-risk result with this test.

Objective: To report our clinical experience and independently confirm that our results with this ABPLA (Pigmented lesion assay, DermTech. San Diego, CA) are consistent with the results of the validation studies completed by the test manufacturer.

Methods: A retrospective review of our electronic medical records for results of ABPLAs, corresponding histopathologic results and available clinical follow-up, along with their statistical analysis was completed.

Results: After reviewing our electronic medical records, we found that 893 ABPLAs for pigmented lesions concerning for melanoma were obtained in a period of 14 months. Of the 893 ABPLAs completed, 161 biopsies and excisions were performed after the initial results of these assays. Additional clinical follow-up data were recorded and used for the statistical analysis of the performance and accuracy of this test.

Limitations: The small number of lesions reported as low risk for melanoma with corresponding histopathologic results limits our evaluation of the performance of this test. In addition, there may have been some melanomas that were not identified because the duration of the clinical follow-up was insufficient or because some patients were lost to follow-up.

Conclusion: In our experience this ABPLA has a sensitivity of 92.0%, a specificity of 79.5%, a positive predictive value of 16.9%, and a negative predictive value of 99.5% for the detection of melanoma.

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INTRODUCTION

The prevalence of melanoma has continued to increase in recent years, and in 2023, the American Cancer Society predicted that approximately 97,610 new melanomas will be diagnosed, and 7990 deaths will result from melanoma in the same year.[1] Alongside the increase in prevalence of this malignant neoplasm, the early detection and consequent treatment is crucial. The importance of early detection has become a factor for the development of new diagnostic techniques, including a commercially available adhesive-based pigmented lesion assay (ABPLA) (Pigmented lesion assay, PLA. DermTech. San Diego, CA). This test is used for lesions that are clinically suspicious for melanoma, which can be sampled using a noninvasive adhesive-based patch.[2] This test utilizes a proprietary process to collect DNA and RNA from the cornified layer of the epidermis.[2] These samples are then used to identify 2 genomic biomarkers associated with melanoma (LINC00518: Long Intergenic Non-Coding RNA 518 and PRAME: Preferentially Expressed Antigen in Melanoma). A second version of the ABPLA is available, and in addition to the detection of PRAME and LINC00518, it also determines the presence of TERT (telomerase reverse transcriptase) DNA promoter mutations.[3] The assay for LINC00518 and PRAME is completed through a process of gene amplification called RT-PCR.[2,4] Through this analysis, it is claimed that excessive expression of PRAME and/or LINC00518 is associated with a higher probability of melanoma.[5] The presence of TERT promoter mutations indicates additional risk and probability of melanoma. In our retrospective study, we found that the PLAs were previously reported by the manufacturer as a "moderate-risk" (if either LINC00518 or PRAME were detected) or a "high-risk" status (if both LINC00518 and PRAME were detected). If both markers were not detected, the test was reported as "low risk" for melanoma. The manufacturer is currently reporting the test as negative if LINC00518 and PRAME are not detected, and positive if either one of these markers is detected. For a negative result, the manufacturer recommends clinical surveillance for changes in appearance. For positive results, the manufacturer recommends considering a biopsy based on

the patient's medical history, clinical evaluation of the lesion, and test results.

The previous studies for this ABPLA reported a sensitivity of 91%–95% and a specificity of 69%–91%. In addition to the reported sensitivity and specificity, this test has a reported negative predictive value (NPV) of approximately 99% and a positive predictive value (PPV) ranging between 15% and 67%, depending on the biomarkers detected.[2,3,6–9] As one of the largest dermatology groups in the country with an in-house pathology laboratory, we have observed a significant increase in the number of ABPLAs performed and found it important to independently confirm that our experience and results with this ABPLA are consistent with the results of the validation studies completed by the manufacturer of this commercially available test.

MATERIALS AND METHODS

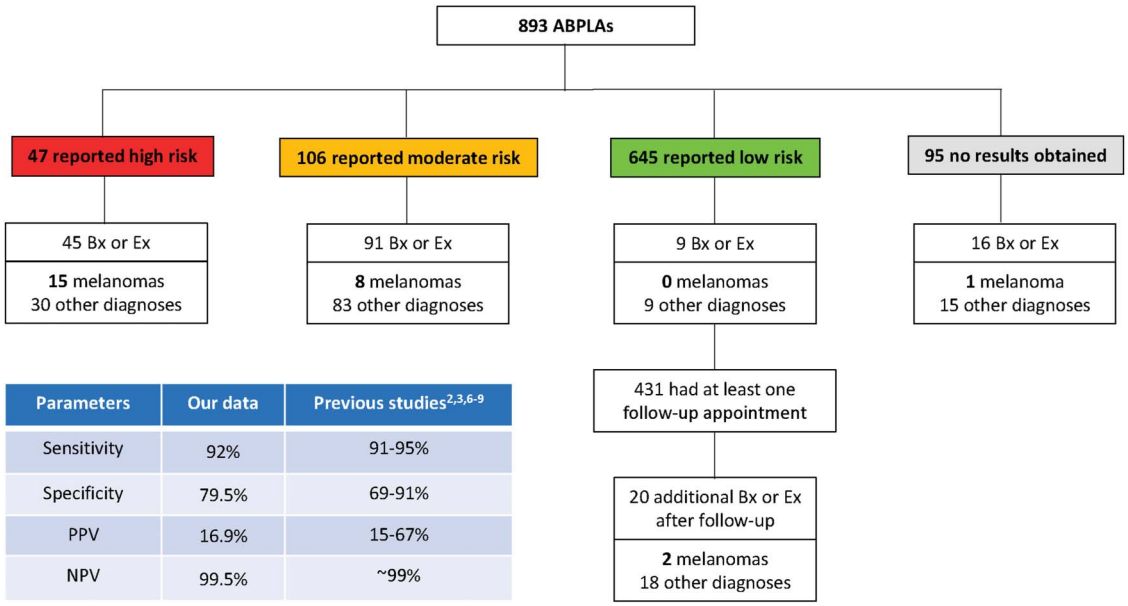
Our study proposal was reviewed by the Institutional Review Board at WCG Clinical Affairs Department who found this study exempt under rule 45 CFR § 46.104(d)(4) of the Code of Federal Regulations and approved a waiver of authorization for the use and disclosure of protected health information. A retrospective review of our electronic medical records was completed to identify all the ABPLAs performed in our patients during a period of 14 months. The ABPLAs performed during this time frame were included in our study, along with their subsequent biopsy results, if applicable.

The results of the ABPLAs and histopathologic diagnoses were recorded and used for the statistical analysis. All the diagnoses of melanoma were confirmed by at least 2 board-certified dermatopathologists. For those ABPLAs reported as low-risk status that had no immediate confirmatory biopsy, our medical records were reviewed looking for subsequent clinical follow-up documenting any significant clinical changes in the pigmented lesion of concern or any subsequent biopsies or excisions, in a similar manner to the process described in previous studies.[7,9] Based on the additional clinical follow-up data available, we assumed that those patients with no documented significant clinical changes and those with a biopsy demonstrating a benign lesion (not melanoma) were true negatives for the subsequent statistical analysis.

The PPV, NPV, sensitivity, specificity, and corresponding 95% bias-corrected bootstrap confidence intervals were computed based on the 576 lesions with both a successful ABPLA and at least one clinical follow-up visit, or a confirmatory biopsy or excision.[10] This analysis was conducted using the *infer* R package.[11] The ABPLAs that did not yield results due to different technical issues were excluded from this analysis.

RESULTS

A total of 893 ABPLAs were found in our medical records during a period of 14 months. For our analysis, these tests were categorized as positive (tests reported as moderate-risk and high-risk status) or negative (tests reported as low-risk status) as explained above. Of these 893 ABPLAs, 161 biopsies and excisions were obtained immediately after the test results and were submitted for histopathologic evaluation by a board-certified dermatopathologist. These results are shown in Figure 1. Of the 47 ABPLAs reported as high-risk status with corresponding biopsy, 9 (19.1%) were diagnosed as melanoma in situ (MIS)/melanoma in situ lentigo maligna type (LM), and 6 (12.77%) were diagnosed as invasive malignant melanoma (MM). For the 106 lesions reported as moderate risk for melanoma, 4 MMs (3.8%) and 4 MIS/



Parameters	Our data	Previous studies[2,3,6-9]
Sensitivity	92%	91-95%
Specificity	79.5%	69-91%
PPV	16.9%	15-67%
NPV	99.5%	~99%

FIGURE 1. Overview of our ABPLA results and comparison of sensitivity, specificity, PPV, and NPV based on our experience and the parameters reported in previous studies of these tests. BX: Biopsy. EX: Excision. MM: Invasive malignant melanoma. MIS: Melanoma in situ/Melanoma in situ lentigo maligna type.

LM (3.8%) were identified. In addition, a basal cell carcinoma was identified in this group. Of the 645 lesions originally reported as low risk, 9 had biopsies right after these test results. Two corresponded to nevi with mild atypia, 2 were benign nevi with no atypia, and 5 were benign nonmelanocytic pigmented lesions such as solar lentigo, benign lentigo, or seborrheic keratosis. For those ABPLAs reported as low-risk status that had no immediate confirmatory biopsy our medical records were reviewed looking for subsequent clinical follow-up documenting any significant clinical changes in the pigmented lesion of concern and any subsequent biopsies or excisions. Of these 636 lesions, 431 had at least one documented clinical follow-up visit to the dermatologist (range from 1 to 21 visits, average of 3.25 visits) with follow-up times ranging between 7 and 854 days (average 448 days) after the initial ABPLA. For 411 of these lesions, no significant clinical change was documented, and no biopsies or excisions were performed. Biopsies obtained from the remaining 20 lesions were submitted for histopathologic evaluation and revealed 2 melanomas (one invasive MM and one MIS), and one basal cell carcinoma. Of the 95 ABPLAs that yielded no results due to different technical issues, 16 biopsies were performed, and one showed a MM (see Fig. 1 and Table 1 for a summary of the histopathologic results following the ABPLAs).

The calculated PPV of the ABPLAs with high-risk status was 33.3%, 95% Cl [22.2%–51.1%], and 8.8% [4.4%–16.5%] for those reported as moderate risk for melanoma. For a combined (moderate and high-risk) PPV of 16.9% [11.8%–24.3%] for those tests considered positive (moderate-risk and high-risk results). The calculated sensitivity, specificity, and NPV were 92% [84.0%–100%], 79.5% [76.2%–82.9%], and 99.5% [99.1%–100.0%], respectively (see Fig. 1 for comparison of our experience with the results of the ABPLA described in previous studies).

DISCUSSION

Being one of the largest dermatology groups in the country, our large number of ABPLAs (893) completed during a 14-month period have allowed us to independently calculate various parameters related to the performance of this commercially available test used for the evaluation of pigmented lesions suspicious for melanoma. As an independent dermatology group, our results are an unbiased summary of our day-to-day clinical experience with this test.

Our calculated values align well with the values previously reported in different studies evaluating this test (Fig. 1). Our estimated sensitivity of 92.0%, 95% Cl [84.0%–100.0%], and specificity of 79.5% [76.2%–82.9%], fall within the previously reported values of a sensitivity of 91%–95% and a specificity of 69%–91%. In addition, our calculated NPV of 99.5% [99.1%–100.0%] also falls within the reported NPV of approximately 99%. Finally, our calculated combined PPV (for tests reported as moderate and high risk) of 16.9% [11.8%–24.3%] is within the previously reported range of PPV between 15% and 67%.[2,3,6–9]

In their reports, the manufacturer describes that this test is intended to rule out melanoma and guide biopsy decisions for pigmented skin lesions that a qualified healthcare provider has assessed as having low-to-moderate probability of being melanoma using established clinical parameters. They also describe that this test is not designed to and does not diagnose melanoma.[2,8,12] It is also worth noting a few limitations regarding the clinical applications of this test. The assay is not intended for lesions considered probable or definitive melanomas, nonmelanocytic lesions, or in areas that have been previously biopsied, excised, or otherwise treated. The ABPLA is not recommended for lesions with a diameter <5 mm or >19 mm, people younger than 18 years, or for samples obtained from palms, soles, nails, mucous membranes, areas with hair that are unable to be trimmed, or lesions that are ulcerated or bleeding.[13] While genital melanocytic lesions are somewhat rare and are reported to be present in only 10%–12% of the population, melanocytic lesions on acral skin are quite common, with an estimated prevalence of 28%–36% in the United States.[14,15]

Some limitations of our calculated NPV should also be noted, as the diagnosis of the lesion of concern was only confirmed by histopathologic evaluation in a very limited number of lesions with a low-risk ABPLA result. We also assumed that patients with no documented significant clinical changes and those with a biopsy demonstrating a benign lesion (not melanoma) were true negatives for our statistical

TABLE 1. Histopathologic Diagnoses in Biopsies or Excisions after ABPLA

ABPLA Results	Total	MM	MIS	Atypical Nevus	Nevus	BCC	Benign Nonmelanocytic	No Bx or Ex
High risk	47	6	9	22	5	0	3	2
Moderate risk	106	4	4	66	13	1	3	15
Low risk	645	1*	1*	15	6	1*	5	616
No results obtained	95	1	0	10	1	0	4	79
Total	893	12	14	113	25	2	15	712

Histopathologic diagnoses by a board-certified dermatopathologist following ABPLAs. These results include a total of 181 biopsies and excisions: 161 biopsies and excisions performed immediately after the initial ABPLA results, as well as 20 additional biopsies performed later after additional clinical follow-up in patients with initial negative/low-risk ABPLAs.

*Of these 20 subsequent biopsies, 2 melanomas (one invasive melanoma and one melanoma in situ) and one basal cell carcinoma were identified. MM: Malignant melanoma. MIS: Melanoma in situ and Melanoma in situ lentigo maligna type. Atypical nevus: includes dysplastic nevi with severe, moderate, and mild atypia, other atypical nevi, and nevi with atypia not graded. Nevus: nevi without atypia. BCC: Basal cell carcinoma. Benign nonmelanocytic: includes lesions such as seborrheic keratosis and lentigo. No BX or Ex: No biopsy or excision was performed. No results obtained: includes insufficient/inadequate material, samples contaminated with hair or blood, samples missing identification, samples labeled incorrectly, and samples too old to process.

analysis. However, there may have been some melanomas that were not identified because the duration of the clinical follow-up was insufficient or because some patients were lost to follow-up.

Finally, an economical evaluation of the test is a key factor in its clinical use. The manufacturer's website reports that the test is covered by several major insurance providers and has $0 out-of-pocket costs for Medicare.[16] It is important to note that in some cases, this test could represent an additional cost for patients and insurance companies on top of the dermatologic consultation and subsequent histopathologic evaluation that is required by some patients. With the conventional approach in which clinical examination of a suspicious lesion by a dermatologist is followed by a biopsy that is evaluated under the microscope by a dermatopathologist, approximately 30 biopsies are required to diagnose one melanoma.[4] Based on our data, approximately 37.2 ABPLAs are required to identify one melanoma (24 melanomas were identified after the initial 893 tests). Furthermore, the ABPLA is a test that reports a risk or probability of melanoma but does not offer a definitive diagnosis required for treatment and prognosis. For those tests reported as positive, a confirmatory biopsy or excision is required to determine the exact diagnosis (MM, MIS, dysplastic nevus, benign lesion, etc.) and to provide fundamental information for the staging and prognosis, such as type of melanoma, depth of invasion, Clark level, ulceration, presence of lymphovascular or perineural invasion, presence of regression, etc.

After reviewing our medical records for additional clinical follow-up for the lesions reported as low risk for melanoma, we found 2 melanomas. The first patient was a 34-year-old woman with a family history of melanoma who presented with a pigmented lesion on her left upper arm in which the initial ABPLA was reported as low risk (no PRAME or LINC00518 detected, and insufficient material for TERT testing). Seven months after the initial ABPLA result, the patient was seen on follow-up, and it was noted that the lesion had noticeably changed. A shave biopsy revealed an invasive MM (pT1a, 0.5 mm in depth, not ulcerated, associated with a nevus). A new ABPLA was performed at the time of the shave biopsy, which then came back as moderate risk (PRAME detected, LINC00518 not detected, and insufficient material for TERT testing). A sentinel lymph node biopsy came back positive for melanoma, and the patient was then put on pembrolizumab. Imaging studies including MRI and PET scan showed no evidence of metastasis to internal organs. The second patient was a 37-year-old woman with a pigmented lesion on her right upper back. This patient had a family history of melanoma and a personal history of previously diagnosed dysplastic nevi. The initial ABPLA was reported as low risk (no PRAME or LINC00518 detected, TERT not detected). Six months after these results, the patient was seen on follow-up, and it was noted that the lesion of concern had changed drastically. A shave biopsy was performed which showed a MIS associated with a nevus. This melanoma was then treated with an excision. Although 2 melanomas were identified on subsequent clinical follow-up visits following a low-risk report with this test, our data show similar results to the previous studies including a NPV >99%. The test manufacturer recommends considering clinical surveillance for changes in appearance for lesions with negative PLAs.

CONCLUSION

The fields of dermatology and dermatopathology are continuously incorporating new technologies into everyday practice. As one of the largest dermatology groups in the country, we aimed to independently assess the performance of an ABPLA used to evaluate cutaneous lesions suspicious for melanoma. Our calculated sensitivity, specificity, NPV, and PPV for the ABPLA closely align with those reported in prior studies. Nevertheless, clinicians should be aware that this test is not recommended in certain specific situations, and these limitations can affect the test's applicability in certain clinical scenarios. Moreover, our calculated NPV for this test is limited by the fact that confirmatory histopathologic evaluation was only conducted in a limited number of lesions with a low-risk ABPLA result. Furthermore, there is a possibility that certain melanomas went undetected due to insufficient clinical monitoring of patients or instances where patients were lost to follow-up. Despite the reported high NPV, 2 melanomas were identified during subsequent clinical follow-up visits after receiving low-risk results with the ABPLA. This underscores the critical importance of continued clinical surveillance, especially in high-risk patients or cases where clinical suspicion remains, to mitigate the risk of overlooking a melanoma following a negative test result.

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