Real-World Utility of a Non-Invasive Gene Expression Test to Rule Out Primary Cutaneous Melanoma: A Large US Registry Study

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ABSTRACT

Introduction: The Pigmented Lesion Assay (PLA) is a non-invasive gene expression test that helps clinicians rule out melanoma via a genomics approach that elevates pigmented lesion management beyond what the eye can see. PLA improves care with a negative predictive value of >99% while reducing biopsies by 90% and while reducing cost.

Methods: The registry study described here (53 US dermatology offices, 90 providers, median patient age 48 years, 60.80% female and 39.20% male patients) assesses real-world utility to determine if the PLA changes clinical practice.

Results: Of 3,418 pigmented skin lesions clinically suspicious for melanoma and assessed by PLA, 324 lesions (9.48%) were PLA(+) and 3,094 (90.52%) were negative. A PLA test result is positive if LINC, PRAME, or both target genes are detected; these molecular pathology findings are known to correspond with histopathology findings of in situ or invasive primary melanoma in 7%, 50%, and 93%, respectively. The 9.48% PLA(+) cases consisted of 5.15% LINC only, 1.93% PRAME only, and 2.40% LINC and PRAME double positive cases. Notably, 97.53% of PLA(+) lesions were surgially biopsied, while 99.94% of PLA(-) cases were clinically monitored and not biopsied.

Discussion: These findings demonstrate that community-based clinicians who employ the PLA to improve pigmented lesion management use the test's results to guide how they practice. Pigmented lesions with PLA(+) test results are subjected to surgical biopsies, whereas PLA(-) lesions are followed clinically and not biopsied.

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INTRODUCTION

Efforts to unambiguously assess and adjudicate primary melanocytic skin lesions clinically suspicious of melanoma to rule out melanoma via the existing standard of care of visual assessment and histopathology remains a challenge even for pigmented lesion experts because of inherent limitations of image recognition.[1-11] Dermoscopy, confocal microscopy, or computer-aided image analysis of skin lesions can reduce some of these inherent limitations. However, these tools generally do not overcome these issues and challenges continue after biopsy decisions have been made. Histologic evaluation is again guided by image and pattern recognition. Histologic criteria to distinguish between benign and malignant are overlapping and are in nature subjective, affecting the performance of our existing mainstay of establishing diagnoses in pigmented lesion management.[4,6] These complexities and issues are highlighted in a large 2017 US study in which Elmore and colleagues assessed the performance of 187 pathologists

and dermatopathologists reviewing the histopathology slides of 240 melanocytic lesions including 118 early-stage melanomas.[4] From the study, the authors estimate that only 82.8% of all melanocytic skin biopsy diagnoses across a population would be verified by a consensus panel of experts. Furthermore, the accuracy of assigning intermediate melanocytic lesions to the correct one of five mPath categories is low, ranging from 25% to 43%.[4] Intra-observer reproducibility showed similarly discouraging discordance.[4] Although an increasing number of studies have demonstrated that immunohistochemistry and molecular analysis techniques, such as fluorescence in situ hybridization, comparative genomic hybridization, and messenger ribonucleic acid (RNA) expression profiling of surgically obtained specimens, can help to somewhat enhance our ability to assess melanocytic neoplasms, these approaches fall short of truly impacting pigmented lesion management because of their performance characteristics and because the tests depend

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on tissue samples from surgical biopsies.[7] Currently up to 90% of all pigmented lesion biopsies are performed on benign lesions and are therefore avoidable.[8] A reliable and actionable non-invasive melanoma rule-out test that guides clinicians' biopsy decisions appears desirable to improve our existing care standard of pigmented lesion management.[12]

The recently described Pigmented Lesion Assay (PLA), a non-invasive PRAME (Preferentially Expressed Antigen in Melanoma) and LINC (Long Intergenic Non-Coding RNA 518) based gene expression assay using an adhesive patch sample collection platform for obtaining epidermal RNA, is such a test.[13-21] The PLA is a comprehensively validated solution characterized by high performance (sensitivity 91-95%, specificity 69-91%, negative predictive value [NPV] >99%) and it has shown encouraging data in utility as well as cost savings.[13-21] We previously reported on real-world utility and up to 12 month follow-up data on PLA(-) tests demonstrating high utility and confirming the test's high NPV.[16] The focus of the current work is to report on our one-year experience of a large US registry study of PLA results and management decisions to further define the test's clinical utility and evaluate how non-invasive gene expression testing to rule-out melanoma and guide biopsy decisions affects how pigmented lesions are managed when the PLA is available.

MATERIALS AND METHODS

We here expand on PLA follow-up and utility findings previously reported that also included long-term follow-up and US registry data; approval was obtained from the Western-Copernicus Group's independent review board.[13,16] We report on a one-year PLA registry study initiated in June of 2018 with data acquisition between July of 2018 and June of 2019. Fifty-three US dermatology practices (and 90 providers within these practices including board certified dermatologists, primary care physicians, physician assistants, and nurse practitioners) participated in the registry and reported on 3,418 pigmented lesions clinically suspicious for melanoma that were evaluated by PLA. The PLA results and management decisions (clinical monitoring of a given lesion or biopsy) were uploaded to a web portal. The web portal supported the collection of PLA results, biopsy decision, biopsy type, and requested 3, 6, or 12-month follow-up if the lesion was marked. Lesion location and patients' sex was also recorded. Potential differences in how board certified dermatologists and other licensed clinicians followed the guidance of the PLA was assessed using the Fisher Exact test in R (Version3.5.1).

All lesion samples were obtained using a non-invasive adhesive skin collection kit (DermTech, La Jolla, CA) according to package insert instructions. In brief, a selected pigmented lesion suspicious for melanoma is cleansed with an ethanol swab and dried, and four adhesive patches from the sample collection kit are applied sequentially to collect one sample. Gentle pressure from about 5 circular thumb motions ensures contact between the

adhesive and skin; no wait time is required. To enable separation of lesional from non-lesional surrounding skin tissue, the lesion is demarcated with a marker pen on each one of the applied adhesive patches. Patches are placed in a pre-addressed courier envelope and shipped to a central processing laboratory without need for refrigeration or special handling. The sample collection process takes about 1-2 minutes. A molecular pathology report is generally available within 48-72 hours.
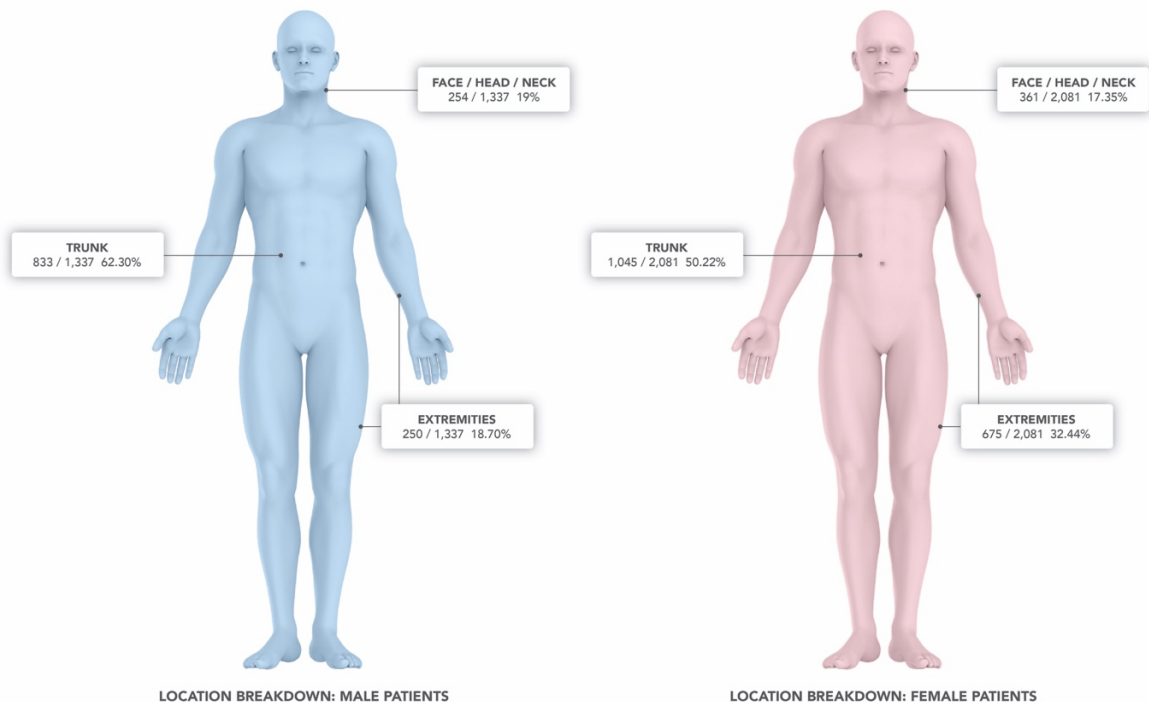
RESULTS

Findings from a large US Pigmented Lesion Assay registry study (53 US dermatology offices, 90 providers) of 3,418 patients and their pigmented skin lesions clinically suspicious for melanoma and evaluated by PLA are presented. The median patient age was 48 years; 60.80% of patients were female and 39.20% were male. Overall, most lesions (55.18%) evaluated by PLA were located on the trunk, followed by locations on extremities (27.27%) and locations in face / head / neck areas (17.55%). Figure 1 provides details on lesion locations in male and female patients demonstrating similar lesion locations in face / head / neck areas (19.00% and 17.35%, respectively) while female patients' pigmented lesions evaluated by PLA were more often located on extremities (32.44% versus 18.70% in male patients).

Of 3,418 pigmented skin lesions clinically suspicious for melanoma and assessed by PLA, 324 lesions (9.48%) were PLA(+) and 3,094 (90.52%) were negative (Figure 2). PLA test results are positive if LINC, PRAME, or both target genes are detected; these molecular pathology findings are known to correspond with histopathology findings of in situ or invasive primary melanoma in 7%, 50%, and 93%, respectively.[14] The 9.48% PLA(+) cases consisted of 5.15% LINC only, 1.93% PRAME only, and 2.40% LINC and PRAME double positive cases (Figure 2). Notably, PLA(+) lesions were surgically biopsied in 97.53% while PLA(-) cases were clinically monitored and not biopsied in 99.94% of the cases. PLA(+) cases with detectable levels of both target genes or detectable levels of PRAME were surgically biopsied in all cases, while 95.45% of LINC-only cases were biopsied (Figure 2).
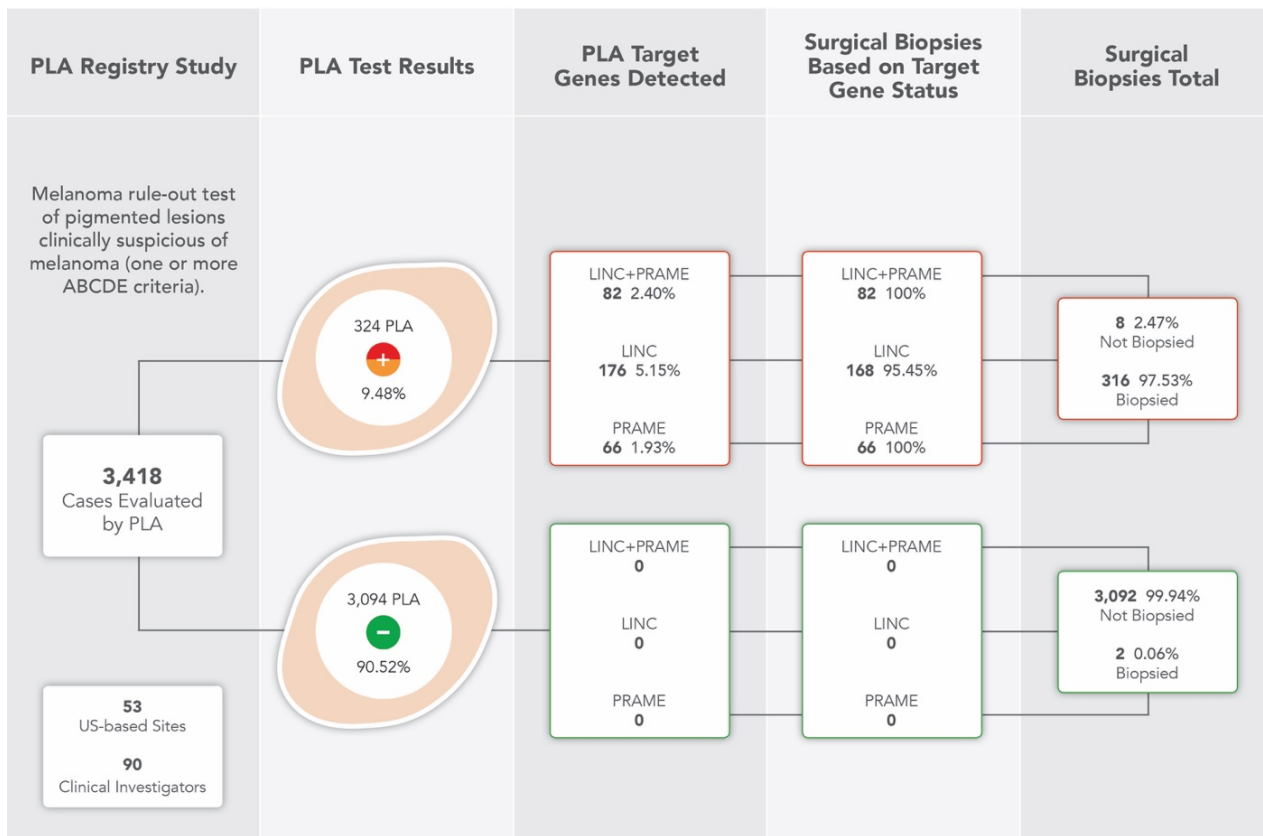
Of a total of 3,094 PLA(-) lesions, only two (0.06%) were subjected to surgical procedures. One was a melanocytic nevus subjected to a shave/scoop biopsy and the second was a squamous cell carcinoma in situ removed by MOHS surgery. The remaining 3,092 PLA(-) cases were monitored clinically and not biopsied or excised. Of these, 179 (5.79%) were scheduled for follow-up in three months, whereas 1,198 (38.75%) and 1,504 (48.64%) were scheduled for follow-up in 6 and 12 months, respectively. In addition, 211 patients (6.82%) were scheduled for follow-up at other time frames.

The vast majority (316 of 324 or 97.53%) of PLA(+) cases (9.48% of all pigmented lesions assessed by PLA in this study), were surgically biopsied as described. Of these biopsies, 51.58% were

FIGURE 1. Anatomical locations of pigmented lesions evaluated by PLA in male and female patients.

LOCATION BREAKDOWN: MALE PATIENTS

FACE / HEAD / NECK
254 / 1,337 19%

TRUNK
833 / 1,337 62.30%

EXTREMITIES
250 / 1,337 18.70%

LOCATION BREAKDOWN: FEMALE PATIENTS

FACE / HEAD / NECK
361 / 2,081 17.35%

TRUNK
1,045 / 2,081 50.22%

EXTREMITIES
675 / 2,081 32.44%

FIGURE 2. PLA registry study outline and a summary on how PLA test results guide biopsy decisions.

PLA Registry Study	PLA Test Results	PLA Target Genes Detected	Surgical Biopsies Based on Target Gene Status	Surgical Biopsies Total
Melanoma rule-out test of pigmented lesions clinically suspicious of melanoma (one or more ABCDE criteria).	324 PLA + 9.48%	LINC+PRAME 82 2.40% / LINC 176 5.15% / PRAME 66 1.93%	LINC+PRAME 82 100% / LINC 168 95.45% / PRAME 66 100%	8 2.47% Not Biopsied / 316 97.53% Biopsied
3,418 Cases Evaluated by PLA	3,094 PLA − 90.52%	LINC+PRAME 0 / LINC 0 / PRAME 0	LINC+PRAME 0 / LINC 0 / PRAME 0	3,092 99.94% Not Biopsied / 2 0.06% Biopsied
53 US-based Sites / 90 Clinical Investigators				

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TABLE 1. Biopsy type after PLA.

	BIOPSY TYPE AFTER PLA				
	Total PLA ⊖	Total PLA ⊕	Total LINC+PRAME ⊕	Total LINC ⊕	Total PRAME ⊕
Biopsy Type after PLA	Shave: 1 (0.03%) Punch: 0 Excision: 1 (0.03%) No Biopsy: 3092 (99.94%)	Shave: 163 (51.58%) Punch: 32 (10.13%) Excision: 121 (38.29%) No Biopsy: 8 (2.47%)	Shave: 23 (28.05%) Punch: 19 (23.17%) Excision: 40 (48.78%) No Biopsy: 0	Shave: 105 (59.66%) Punch: 19 (10.80%) Excision: 44 (25.00%) No Biopsy: 8 (4.55%)	Shave: 24 (36.36%) Punch: 4 (6.06%) Excision: 38 (57.58%) No Biopsy: 0

shave/scoop, 10.13% were punch, and 38.29% were excisional procedures. Table 1 summarizes the types of biopsy procedures employed and provides further details on how not only PLA results, but the detection of either one or both of the target genes affects the type of biopsy procedure selected. All 8 PLA positive cases not subjected to biopsies were LINC-only cases, which have a lower probability of being melanomas histopathologically.[14] There was no significant difference in how board certified dermatologists (n=2,146 submitted cases) and other licensed clinicians (primary care physicians, physician assistants and nurse practitioners; n=1,272 submitted cases) follow the guidance of the PLA based on assessing the proportion of biopsies ordered as follow-up for either PLA(+) or PLA(-) specimens (P=0.11 and P=0.29, respectively).

The PLA is positive if either LINC or PRAME or both LINC and PRAME are detected. LINC positive, PRAME positive and LINC and PRAME double positive cases correlate with a histopathologic diagnosis of melanoma in 7%, 50%, and 93%, respectively.[14]

DISCUSSION

The PLA is a non-invasive melanoma rule-out test that guides biopsy decisions and helps clinicians ascertain genomic risk factors the eye cannot see. Key to a highly performing rule-out test is a high negative predictive value or NPV, a measure that assesses the probability that a negative test result is indeed correct. Previous studies confirm that the PLA has a predicted NPV of >99%.[13-15,21] The current registry study was undertaken to understand how clinicians' real-world management of pigmented skin lesions changes with use of PLA gene expression data and to further confirm the rule-out test's NPV. Earlier findings from a separate study of 734 PLA(-) lesions reviewed at 12 months demonstrated that only 1.8% of PLA(-) lesions were biopsied in this follow-up period. None of the lesions biopsied had a melanoma diagnosis by histopathology consistent with PLA's high NPV.[16] Pigmented lesions suspicious for melanoma and clinically followed often manifest visible changes, such as size increase or border and color changes within 12 months also reflected in the follow-up periods selected by clinicians in this registry study.[1,22-26] The PLA performance relative to blinded consensus reads (91% sensitivity) compares favorably to primary site histopathology performance (84% sensitivity).[13,21] The PLA

furthermore reduces the number needed to biopsy (NNB, the number of biopsies needed to detect a melanoma) by a factor of about 10 from 25 to 2.7.[7,14,21] Cost savings of the PLA are primarily driven by a reduction in initial biopsies and excisions as well as reduced stage-related treatment costs from missing fewer melanomas.[20]

The 90 participating US clinicians (board certified dermatologists, primary care physicians, physician assistants and nurse practitioners) used the PLA widely in all appropriate anatomical areas that harbored pigmented lesions of concern rather than in cosmetically sensitive face / head / neck areas as the non-invasive nature of the test may have led to believe. The PLA was used twice as often in female compared to male patients; the median age of PLA patients was 48 years. Over 90% of PLA registry study test results were negative in line with about 90% of surgical biopsies being performed on benign lesions and PLA(-) patients avoided biopsies and other surgical procedures.[8] In the presented registry study, 99.94% of PLA(-) cases were scheduled for follow up surveillance and not biopsied. Only two of 3,094 PLA(-) lesions (0.06%) were not observed but biopsied or excised. One was a nevus that was biopsied, and the other lesion was a squamous cell carcinoma in situ removed via MOHS surgery where the PLA may have been used to rule out melanoma prior to selecting a MOHS procedure. There is clear clinical benefit to patients assessed by PLA who avoided surgical biopsy procedures as well as risks of scarring, infection, bleeding, and abnormal wound healing, which may occur in a small subset of patients, but which is magnified by the high number of surgical pigmented lesion biopsies.[7,21] Perhaps even more importantly, initial surgical biopsy procedures often lead to wider margin excisions due to uncertainty of the initial histopathologic diagnosis. This phenomenon is linked to challenges associated with histopathologic assessment, including limited lesion sampling of only 1-2% of the biopsied tissue, overlapping diagnostic criteria between atypical nevi and early stage melanoma, and variability in the assessment of cellular atypia.[4,6,27,28] These wide excisional procedures are much more significant and often require closure repair. Up to 65% of initial biopsy procedures may be followed with a wider margin excision. Therefore, reducing initial surgical biopsies has the added clinical benefit of reducing follow-up full excisions.[27]

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It is of equal importance to ensure that PLA(+) tests are appropriately followed with surgical biopsies. In the reported registry study, 97.53% of PLA(+) cases were biopsied. Only 8 of 324 PLA(+) registry study cases (0.06%) were not biopsied but rather monitored and all 8 were LINC-only positive. Tests with this single transcript only carry a lower probability of being diagnosed histopathologically as melanomas than tests with the PRAME transcript only, or results with both transcripts detected.[14] Previous studies established that 93% of PLA results positive for both LINC and PRAME are diagnosed histopathologically as in situ or invasive melanomas. PRAME positive only and LINC positive only lesions are melanomas histopathologically in 50% and 7%, respectively.[14] Both targets are known to be overexpressed in melanoma and mechanistically PRAME promotes melanoma progression by interfering with retinoic acid receptor signaling and LINC is a regulator of oncogenesis affecting melanoma proliferation and invasion.[13] All PRAME-only or LINC and PRAME double positive cases were biopsied at all registry study sites. More excisional biopsies were performed on double positive lesions and PRAME positive lesions, which have a higher probability of being diagnosed as melanomas by histopathologic assessment than on LINC-only lesions, as detailed in Figure 2 and Table 1. Overall, the types of biopsies conducted were consistent with US practice favouring shave / scoop procedures (Table 1).

The present standard of care for the management of atypical pigmented skin lesions focuses on efforts to rule out melanomas via clinical visual assessment followed by surgical biopsies and again visual assessment of dermatopathologic features.[1-11] The objective of this assessment is to identify melanomas at their earliest stages when a high cure rate is possible by wide excision while clinically monitoring lesions that don't need to be biopsied.[22] The existing visual standard of care pathway has a NPV for early stage melanoma ranging from 75%-89%,[4-8] although real-world performance can be higher due to a default to wide excisions in challenging cases and the use of special stains of lesions with difficult pigmented lesion pathology. The PLA provides an alternative assessment route for clinicians who manage pigmented skin lesions that demonstrates a high NPV (>99%) while reducing surgical procedures of benign lesions by 90%. Notably, there is also growing evidence that not only clinicians, but also dermatopathologists benefit from the availability of melanoma-associated molecular risk factor information as primarily image recognition-based assessment of pigmented lesions remains challenging even for experts.[16,24] Findings from this large registry study establish that clinicians across a spectrum of 53 US-based sites that manage pigmented lesions, appropriately follow the guidance of the test. PLA use is not limited to cosmetically sensitive areas.

CONCLUSIONS

Findings from a large US Pigmented Lesion Assay (PLA) registry study on 3,418 cases of pigmented lesions clinically suspicious

of melanoma and assessed by PLA confirm the PLA's high clinical utility and high negative predictive value. Clinicians follow the guidance of the test and rely on its performance. PLA(-) lesions are monitored clinically and generally not biopsied, avoiding unnecessary surgical procedures; PLA(+) lesions are biopsied as intended. The PLA is a test that transforms the existing diagnostic pathway from one that is subjective, invasive, and of lower accuracy to one that is objective, non-invasive, and highly accurate.

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