DermTech

PIGMENTED LESION ASSAY (PLA)

Clinical Utility and Technical Assessment

The test helps dermatologists rule out melanoma and the need for surgical biopsy of atypical pigmented lesions, melanocytic in origin, with a suspicion for melanoma, having 1 or more ABCDE criteria. The test reduces unnecessary surgical procedures while minimizing the risk of missing melanoma (NPV>99%). The test utilizes a non-invasive adhesive patch sample collection device and analyzes the expression of two genes (PRAME and LINC00518), which are elevated in melanoma. The test result is binary (positive/negative) based on detection of gene expression of one or both genes.

CURRENT CARE-PATHWAY OVERVIEW

The estimated prevalence of pigmented lesions (moles) ranges from 2% to 8% in fair-skinned persons. (1,2) Pigmented lesions may be classified as clinically atypical by meeting one or more of the American Cancer Society's ABCDE criteria (Asymmetric, irregular Border, variegated or dark Color, Diameter >6 mm, Evolving mole). Atypical pigmented lesions are at risk for harboring melanoma. A meta-analysis of case-control studies found that the relative risk of melanoma is 1.45 in patients with one atypical mole vs. none, and this increases to 6.36 in those with five atypical moles. (3) Management of atypical pigmented lesions involves ruling out melanoma via a visual assessment followed by surgical biopsy and histopathology. Ideally, when melanomas are identified, they are found at the earliest stages (Melanoma in Situ (MIS)/ Stage 1a) when a high cure rate is possible by wide excision. (4) Since a biopsy only partially removes a lesion for histopathologic analysis, early stage melanoma diagnoses are treated with a follow up wide excision procedure (0.5-1.0 cm margins).

CURRENT CARE-LOW NEGATIVE PREDICTIVE VALUE

While the purpose of the visual assessment and histopathology is to rule out melanoma, the poor performance metrics of this diagnostic pathway lead to a low negative predictive value (NPV) for early stage disease (Figure 1). Because the clinical criteria used during the visual assessment are subjective and non-specific, a high number of biopsies are performed on benign atypical nevi. The real-world specificity of the visual assessment ranges between 3% and 10%*. (5-10) During the subsequent histopathologic assessment, a small number of melanomas must be identified from this large pool of biopsied atypical nevi. However, there is significant overlap in the histopathologic diagnostic criteria between atypical nevi and early stage melanoma invariably leading to false negative diagnoses and a relatively low sensitivity (65%-84%). (10,11,12,13) With the prevalence of early stage melanoma in biopsied lesions at approximately 5%, the negative predictive value ranges from 75%-89%.(9,22)

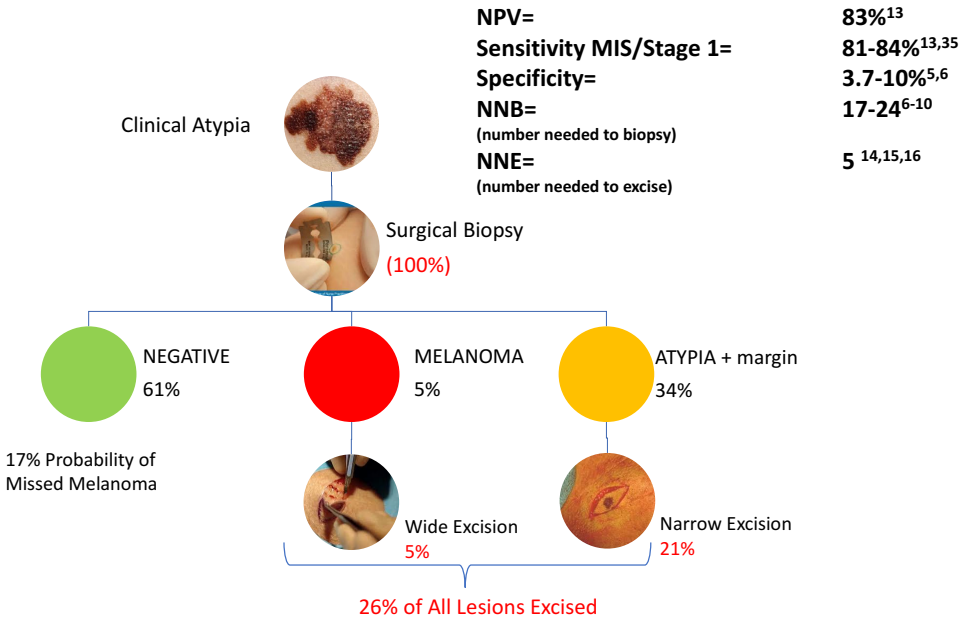


Figure 1 shows the current pathway for pigmented lesion management consisting of visual assessment followed by surgical biopsy and histopathology. 100% of atypical pigmented lesions in this pathway are biopsied resulting in 26% of all lesions being excised with margins. The Number Needed to Biopsy (NNB) averages 20 and the Negative Predictive Value (NPV) is 84% indicating a high probability of missed melanoma.

The poor performance of histopathologic assessment of early-stage melanoma and melanocytic lesions is exemplified in a 2017 study by Elmore et al. (12) In this study 187 pathologists reviewed histopathology slides of 240 melanocytic lesions with 118 diagnosed as early stage melanoma (MPath-Dx Class III (MIS) and Class IV (Stage 1a invasive). The primary pathologists' diagnosis was compared to a consensus diagnosis made by a dermatopathologist panel. Overall the sensitivity of diagnosis for MIS/Stage 1a melanoma was 65%, with 54% of Class III MIS lesion slide interpretations (1,215/2,247) and 15% of Class IV Stage 1a lesion slide interpretations (326/2169) underdiagnosed as false negative benign lesions (see Table 5 of the Elmore paper).This data yields an NPV consistent with the ranges given previously (75%-89%). In addition, 11% (241/2277) of benign lesion slide interpretations were overdiagnoses of melanoma leading to concerns of overtreatment and expert referral. The authors concluded that the diagnosis of early stage melanoma was neither accurate nor reproducible.

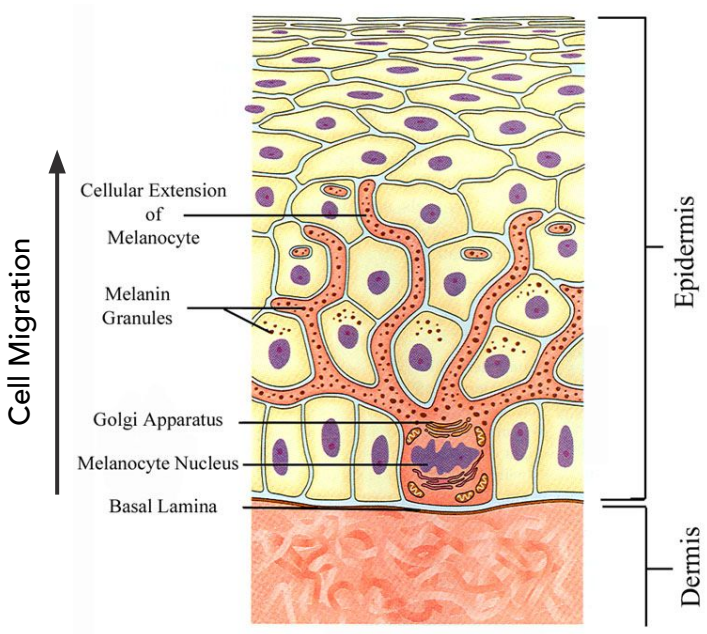
Additional studies support the notion that the real NPV of the visual assessment/histopathology pathway is likely in the low to mid 80% range, again driven by the low specificity and sensitivity. In Malvehy et al., 206 MIS and Stage 1a (thickness<0.75 mm) melanomas were subjected to a consensus histopathologic diagnosis by dermatopathologists. (13) Similar to Elmore, the consensus read was compared to the primary site read, and it was found that only 166 lesions were diagnosed as melanoma by the primary site yielding a sensitivity of 81%. In a similar analysis by Hornberger et al., 128 early stage melanomas with a consensus read were compared to the primary read and only 108 were correctly diagnosed at the primary site, yielding a sensitivity of 84%. (35) In the Malvehy study, 1,943 pigmented lesions were biopsied to find the 206 early melanomas, yielding a specificity of 10%, a melanoma prevalence of 10%, and an NPV of 83%.§ While the specificity cannot be derived from the Hornberger data, using data from the literature gives a calculated NPV of 85%-89%. Overall this data indicates that the NPV for early stage melanoma of the visual assessment and surgical biopsy/histopathology pathway is approximately 83%-89%, such that there is a high (11%-17%) probability of missing melanoma.

CURRENT CARE-UNNECESSARY SURGICAL PROCEDURES

This low NPV for the current care pathway is accompanied by a high number of unnecessary surgical procedures, again driven by the poor specificity of the visual assessment. (5) The number of surgical biopsies needed to identify one melanoma (NNB, number needed to biopsy) averages 20-24 and ranges from 8 to greater than 30 depending on the setting. (5-10) In a recent study by Anderson et al. (2018), 8,078 pigmented lesions were evaluated for NNB by dermatologists and nurse practitioners. (9) The NNB for dermatologists was 25 and the NNB for nurse practitioners was 39. The most common biopsy procedure is a tangential or shave, which does not typically sample all margins of a lesion. (16) Further, the histopathologic review of biopsied lesions is extremely limited with 2% or less of the lesion sectioned and evaluated, leaving doubt as to what may be occurring in the rest of the lesion. Consequently, lesions that have cellular atypia and positive margins are often clinically managed conservatively and subjected to full excisions with margins. (14,15,16) However, only 0.2% to less than 1.0% of lesions with atypia and positive margins that undergo excision are diagnostically upgraded, most commonly to a higher level of atypia and rarely to melanoma in situ, and can be considered unnecessary. (14,15,16) Approximately 5.2 excisions with margins are performed per melanoma identified, emphasizing how the current pathway of surgical biopsies and limited histopathology assessment leads to more complex and invasive surgical excisions. (14,15,16) It is estimated that 3.0 million surgical biopsies and 780,000 excisions were performed in 2017 to find approximately 150,000 melanomas as part of the current diagnostic pathway for atypical pigmented lesions. (17,18)

PIGMENTED LESION ASSAY (PLA)-OVERVIEW

The Pigmented Lesion Assay (PLA) is a gene expression test that helps clinicians rule out melanoma and the need for a surgical biopsy of atypical pigmented lesions (Figure 2). The PLA is based on a new platform technology for non-invasive genomic testing of the skin that allows the analysis of samples collected with an adhesive patch. Four patches are placed on a lesion. For each patch, the margin of the lesion is outlined by the clinician. This outlined tissue is dissected away from the surrounding tissue by the processing lab, and the RNA is extracted only from the lesional tissue. (24)



In contrast to histopathologic sectioning, this method of tissue sampling allows the collection of tissue from the entire lesion. Further, genomic information obtained by adhesive patch sampling of the stratum corneum contains information from deeper epidermal cells. This is the result of natural skin physiology in which basal cells migrate up to the surface of the skin as they differentiate into squamous cells. During this process, keratinocytes acquire melanosomes from melanocytes through a phagocytic process of the melanocyte dendrite. In addition, some melanocyte cells migrate to the skin surface (pagetoid spread). Consequently, epidermal sampling with an adhesive patch yields genomic material from a variety of cells, including melanocytes, keratinocytes, and immune cells.

PLA-INTENDED USE

The PLA test is intended for use by dermatologists in patients 18 years or older, with pigmented lesions suspicious for melanoma, meeting one or more ABCDE criteria. It is not intended for use on clinically diagnosed or obvious melanoma. It is not intended for use on non-melanocytic lesions (e.g. seborrheic keratosis), including non-melanoma skin cancers (e.g. basal cell carcinoma). The test should not be used on bleeding or ulcerated lesions. The PLA cannot be used on the palms of the hands, soles of the feet, nails, or mucous membranes. The PLA is used to aid the surgical biopsy decision, and not as a diagnostic test for melanoma. Positive PLA tests are followed up with a surgical biopsy, most commonly a tangential shave, while negative tests are scheduled for surveillance per standard of care.

PLA VS. CURRENT CARE

In contrast to the current pathway, the PLA has a very high negative predictive value (>99%) and high sensitivity (91-95%), ensuring a very low probability of missing melanoma. (19,20) The high specificity (69%-91%) effectively reduces the number of false positive samples undergoing histopathology review. This improves the overall sensitivity of the pathway and greatly increases the NPV. In addition, the non-invasive sampling leads to a dramatic reduction in surgical biopsies and subsequent excisions. Consequently, the NNB using the PLA is markedly reduced to 2.7 and the number of excisions needed is reduced to 1.6 (Figure 3). (20) Overall, with the PLA, unnecessary surgical procedures are reduced by ~88%. (21) This data is consistent with a recent (2017) review of 18,715 biopsied pigmented lesions that found that 83% of these lesions were benign or mildly atypical lesions and did not need a biopsy, with an additional 8.3% diagnosed as moderately to severely atypical. Thus, ~90% of surgical biopsies performed on pigmented lesions are negative and unnecessary. (21,22)

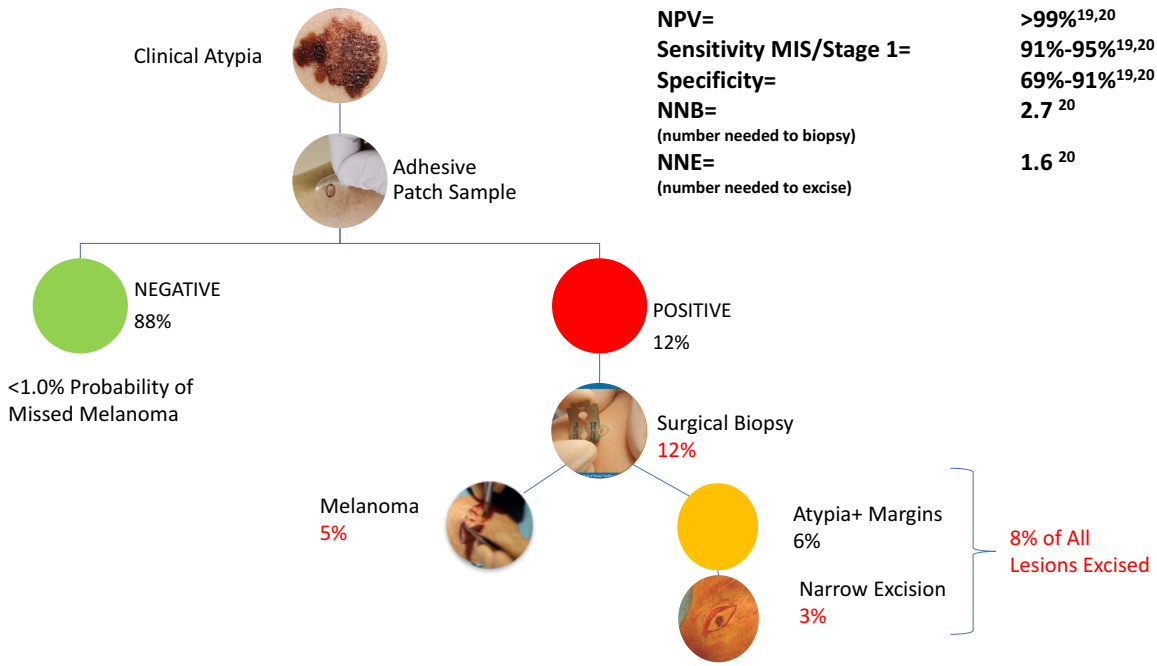
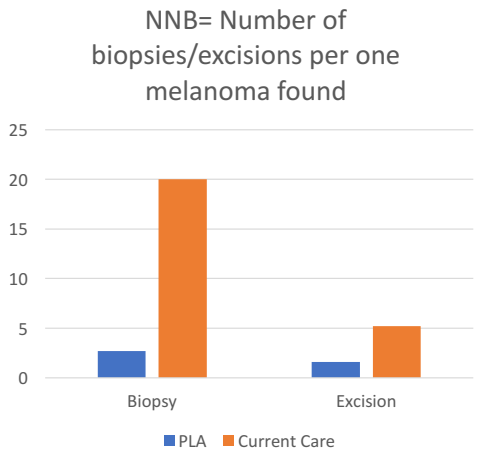


Figure 2 shows the PLA pathway for managing pigmented lesions. Only 12% of pigmented lesions are surgically biopsied using the PLA resulting in only 7% of all lesions excised with margins. The NNB of this pathway is 2.7 and the NPV is 99% indicating a low probability of missed melanoma.

PATIENT BENEFIT

The reduction in unnecessary surgical procedures (biopsies and excisions) has significant benefits to patients by avoiding the morbidity, scarring, and downtime associated with surgical procedures. In addition, significant benefits accrue to the healthcare system with the PLA by reducing costs associated with unnecessary surgery. Even more importantly, the probability of missing melanoma, which may have the most severe consequences, is lower with the PLA relative to the current pathway. The PLA provides a unique clinical value proposition in the assessment of pigmented lesions, transforming the current pathway from a subjective, invasive, and low accuracy paradigm, to one that is objective, non-invasive, and highly accurate.

PLA REDUCES UNNECESSARY SURGICAL PROCEDURES



PLA REDUCES MISSED MELANOMA

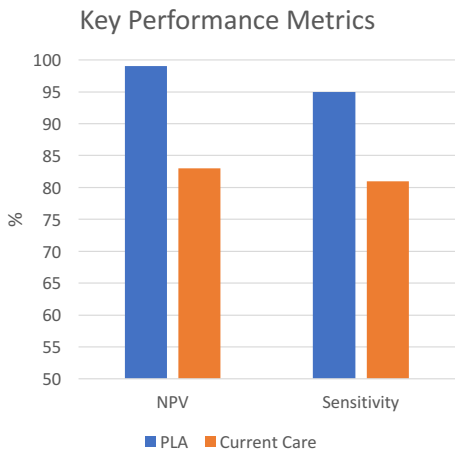


Figure 3 summarizes the key improvements that the PLA demonstrates over the current care standard of surgical biopsy and histopathology. The PLA significantly reduces the number of biopsies and excisions needed to identify early stage melanoma and has a significantly higher NPV ensuring that few melanomas will be missed.

PLA VALIDATION AND CLINICAL TESTING

The performance of the PLA is supported by 9 investigational studies and 6 publications, with 2 additional manuscripts accepted and 1 under review. Table 1 summarizes the publications/manuscripts and key findings of these studies. (13-20) The Level of Evidence supporting the PLA is strong with all studies meeting design criteria consistent with standard methodologies used to validate molecular diagnostic tests, consistent with tests that have received favorable coverage decisions, and consistent with mCTD designation criteria of 3B and 2A, per Medicare MolDX guidelines. The PLA's clinical studies have included meaningful numbers of patients/samples (total >1,500) and clinicians (>50) from which strong statistical analyses can be performed, and several methods of validation have been employed. The clinical settings, inclusion/exclusion criteria, and lesion stage are consistent across studies and consistent with the intended use population. Importantly, utility studies demonstrate the test favorably and dramatically improves patient management.

TABLE 2: PLA PUBLICATIONS AND MANUSCRIPTS UNDER REVIEW

	Published Studies and Manuscripts under Review Involving the Pigmented Lesion Assay (PLA)
1. Analytical Validation	Yao Z, et al. (2016). "Analytical Characteristics of a Noninvasive Gene Expression Assay for Pigmented Skin Lesions." ***Assay and Drug Development Technologies*** 14.6 (2016): 355-363. (23)
2. Clinical Validation	Yao Z, et al. "An Adhesive Patch-Based Skin Biopsy Device for Molecular Diagnostics and Skin Microbiome Studies." ***Journal of Drugs in Dermatology*** 16.10 (2017): 611-618. (24)
3. Clinical Validation	Gerami P, et al. "Development and validation of a noninvasive 2-gene molecular assay for cutaneous melanoma." ***J Am Acad Dermatol*** 76.1 (2017): 114-120. (19) • *398 validation samples, 157 training samples.* • *PLA performance accuracy: 91% sensitive and 69% specific, NPV 99%*
4. Clinical Validation (supplemental)	Ferris L, et al. "Validation of Noninvasive Gene Expression (PLA) Against High Risk Driver Mutations (BRAF, NRAS, and TERT) in Cutaneous Melanoma. Accepted late breaking abstract JAAD, ***Journal of Investigative Dermatology***, under review. 2018 (25, 26-33) • *103 Pathology confirmed samples: 86% of PLA-/Histo- lesions were mutation negative, statistically significant differences in mutation frequency in PLA+/pathol+ samples versus PLA-/pathol- samples (77% vs. 14% p<<0.0001).* • *519 real-world PLA+ and PLA- test results were also analyzed for mutations. 88% of real-world PLA- results were mutation negative and consistent with the validation set indicating negative lesions have few mutational risk factors.*
5. Clinical Utility	Ferris L, et al. (2017). Real-World Performance and Utility of a Non-Invasive Gene Expression Assay to Evaluate Melanoma Risk in Pigmented Lesions. ***Melanoma Research***, Accepted. (20) • *Analysis of 381 patients, yielding 51 PLA+ and 330 PLA- tests.* • *PLA sensitivity 95%, specificity 91%.* • *The test guides clinical management of lesions:* • *99% of PLA- tests underwent surveillance pathway* • *100% of PLA+ tests received biopsy* • *Zero missed melanomas in the follow up period* • *Number of biopsies needed per melanoma found 2.7* • *Number of excisions needed per melanoma found 1.6* • *Visual assessment/histopathology pathway sensitivity 84%*
6. Clinical Utility	Ferris et al. (2017) Utility of a noninvasive 2-gene molecular assay for cutaneous melanoma and effect on the decision to biopsy. ***JAMA Dermatology*** 153:675-680. (34) • *45 dermatologists evaluated 60 clinical and dermatoscopic images plus patient and lesion history.* • *Both sensitivity and specificity improved with PLA results over clinical evaluation alone (specificity 32%→57%; sensitivity 95%→99%).*

7. Clinical Utility/ Economic Impact	Hornberger J and Siegel D (2018) Economic impact of the PLA on the assessment of pigmented lesions. ***JAMA Dermatology***, Accepted, pending final review (35) • *Cost reductions of $395 in surgical procedure costs and $433 in stage related treatment costs*
8. Clinical Validation	Jansen et al. (2018) Gene expression analysis differentiates melanomas from Spitz nevi. ***J Drugs Dermatology*** volume 17, in press (36) • *PRAME normalized expression levels in pediatric melanoma significantly higher (p<0.001) than in common nevi and Spitz nevi (FFPE tissue blocks, n=23)* • *Pediatric melanomas (mean Ct 33.83 ± 0.54, 95% CI 32.85-34.80)* • *Spitz (37.21 ± 0.98, 95% CI 35.41-39.01)* • *Common nevi (36.94 ± 0.80, 95% CI 35.47-38.40)*
9. Proof of Concept	Wachsman et al. (2011) Noninvasive genomic detection of melanoma. ***Br J Derm*** 164:797 • *Microarray whole genome screen for differential expression between nevi and melanoma.* • *Target genes identified for assay development*

DEVELOPMENT/PROOF OF CONCEPT

The PLA was developed by conducting a whole genome screen using microarray technology to identify highly differentially expressed genes between early stage cutaneous melanoma, atypical nevi, and normal skin. (37) Hierarchical gene clustering of 312 genes demonstrated two main branches separating melanoma from atypical nevi and normal skin. Normal skin tended to cluster with nondysplastic nevi. This data suggested that melanoma could be separated from nevi and normal skin through adhesive patch sampling of stratum corneum. (37)

Class prediction modeling was subsequently used to train a gene classifier to discern melanoma from non-melanoma. This classifier was applied to an independent test set and was found to separate melanoma from non-melanoma with a high sensitivity and specificity. Subsequent testing and transition to a qPCR platform indicated that the classification between melanoma and non-melanoma was driven primarily by PRAME and LINC00518. Because both genes are overexpressed in melanoma, a binary reporting scheme based on detection of gene expression (one or both genes), using a fixed input of RNA, could be utilized for the assay now known as the PLA.

PRAME is a highly specific cancer biomarker originally discovered in melanoma (the M in PRAME stands for melanoma). (38) PRAME is also a key biomarker used in two other commercial melanoma tests. PRAME was granted a coverage decision for ocular melanoma prognosis by MolDX in 2017. (39) LINC is part of a new class of regulatory RNAs that are gaining prominence in cancer biology as gene expression regulators. (40)

CLINICAL VALIDATION AGAINST HISTOPATHOLOGY

The performance metrics of the PLA were validated by Gerami et al., J Am Acad Dermatol, 2017, and clearly demonstrate the test's clinical validity in the assessment of challenging early stage pigmented lesions. (19) In this IRB approved study, samples were collected prospectively from multiple dermatology practices and centers, in patients 18 years of age or older, and from pigmented lesions that were suspicious for melanoma, meeting one or more ABCDE criteria. Clinically obvious or frank melanomas were excluded. Lesions were simultaneously sampled using the adhesive patch and surgically biopsied. Biopsy specimens underwent pathologic diagnosis from 3 independent dermatopathologists, and lesions that received a concordant diagnosis from all 3 dermatopathologists were enrolled in the study. Overall, 11% of lesions sampled had a discordant pathological read and were excluded. A blinded evaluation of these concordant biopsy samples was performed against the PLA result.

An initial training set of 157 lesions was tested and demonstrated a 91% sensitivity, 53% specificity. An independent validation set was subsequently studied that included 398 pigmented lesion samples (87 melanomas, 253 atypical pigmented lesions, 53 non-melanocytic lesions). All melanomas enrolled in the study were classified as very early stage and were either MIS or Stage 1 with a median Breslow thickness <0.5 mm. The PLA demonstrated a high sensitivity (91%), a high specificity (69%). The lower bound of the confidence interval for sensitivity was 83%, with an upper bound of 96%, indicating that the PLA performs at least as well as, and is likely much better, than the surgical biopsy pathway for this metric (5,35). In real world routine use US dermatology office settings, the sensitivity of the PLA has been shown to be 95%. (20) This study had a very high prevalence of melanoma (21%), yet even at this enriched prevalence number the NPV is 97% and meaningfully higher than the current pathway. At a more realistic prevalence of 5%, the NPV is calculated at >99%.

CLINICAL UTILITY REAL-WORLD

A review of ~15,000 commercial PLA results indicated that 88% of reported PLA tests were negative and 12% were positive. (21) This is consistent with a recent (2017) study of 18,715 surgical biopsies of pigmented lesions showing that ~83% of the lesions biopsied were either benign or mildly atypical lesions, with an additional 8.3% moderately to severely atypical. Thus, ~90% of biopsies performed are negative and unnecessary. (22)

We subsequently undertook an IRB approved case review study to look at performance, outcomes and clinical management decisions for PLA- and PLA+ cases at 4 dermatology practices using the PLA commercially. Cases were reviewed with a minimum of 3 months to 6 months follow-up. Serial dermatoscopy studies indicate that melanomas have detectable visual changes within 3 months and recommended surveillance guidelines are 3-6 months. (41) For the 381 lesions evaluated in this study, the sensitivity was 95% and the specificity was 91%. While the sensitivity in this study is similar to that found in the histopathologic validation, the specificity is increased. This increase in specificity may be attributable to differences in clinical study versus real world settings, such as a lower prevalence of melanoma in biopsied lesions.

Ninety-nine percent (99%) of 330 PLA- lesions were appropriately managed by dermatologists with surveillance. Three (3) of the PLA- lesions biopsied in the follow up period were done so at the patient's insistence. One (1) PLA- lesion was simultaneously surgically biopsied and adhesive patch sampled, and was diagnosed as melanoma in situ. There were zero missed melanomas found in the follow-up period, confirming the high negative predictive value and low false negative rate.

One hundred percent (100%) of 51 PLA+ test results were appropriately managed by dermatologists with surgical biopsy. Nineteen (37%) of these cases were MIS/Stage 1 melanomas with a thickness of <0.5 mm and demonstrating a NNB of 2.7 (51/19). The number of excisions performed per melanoma found was 1.6 (30/19). The prevalence of melanoma in this study was 5.0% (19/381) consistent with the prevalence of melanoma in surgically biopsied pigmented lesions, and demonstrating a real-world NPV >99%. Ninety-two (92%) of PLA+ lesions were atypical melanocytic lesions with 22% moderately/severely atypical and 27% mildly atypical. This data indicates that a positive PLA result appropriately identifies lesions for biopsy. Equally important, these findings demonstrate that clinicians follow the guidance of the test.

CLINICAL UTILITY READER STUDY

In a study by Ferris et al., 45 dermatologists who regularly evaluate pigmented lesions, assessed 60 cases containing dermatoscopic and lesional images (8 melanoma and 52 nevi with know pathologic concordance) with full patient and lesion history. (34) The photographic/dermatoscopic analysis design of this study provided information nearly identical to the dermatologist's primary clinical visual assessment used to make biopsy decisions, and is therefore more relevant than typical decision impact studies that involve select case information review with and without a test result. Cases/images were initially presented without PLA results, and the dermatologists were asked to make a biopsy decision for suspicion of melanoma. The 60 cases were then shuffled and presented again, including the PLA test data. Again, dermatologists were asked to make a biopsy decision for suspicion of melanoma. Outcomes included changes in biopsy decisions, specificity, and sensitivity. Correct biopsy decisions increased from 750 to 1331. The baseline specificity was higher than in the real-world due to the make up of the reading physicians who were pigmented lesion experts and the presentation of detailed dermatoscopic images. Nonetheless, the specificity of the biopsy decision increased by 1.8-fold with the PLA (32%-56%, $p<0.001$). The baseline sensitivity of readers in this study was also high (95%), which is due to the study design in which there is a finite number of melanomas (8) which are likely to be biopsied due to the low specificity. However, the sensitivity improved to approximately 99% ($p=0.01$) with the PLA, even with significant increases in specificity. Overall this study demonstrated that even board certified pigmented lesion experts biopsy about half as often while missing fewer melanomas when the PLA is included in the biopsy management decision.

ECONOMIC IMPACT AND CLINICAL UTILITY

The economic impact of the PLA, using real-world utility data, has also been characterized. In a study by Hornberger et al., a health economic analysis was performed from a US payer perspective based on consensus treatment guidelines and CMS fee schedules. Data sources for model input were derived from routine use of the test in US dermatology practices. The primary analysis was the relative reduction in costs of diagnostic surgical procedures for PLA versus visual assessment and surgical biopsy/histopathology management. Additional analyses included stage-related treatment costs associated with delays in diagnosis (e.g. surgical costs, immunotherapy, and targeted therapy). The high specificity and low NNB of the PLA lower relative direct medical costs related to the initial surgical diagnostic biopsies and excisions by $395. In addition, follow-up surveillance costs were reduced by $119. The higher sensitivity/NPV reduces delays in diagnosis and lowers costs of stage-related disease management by $433. Overall the relative cost reduction of the non-invasive PLA was $947. Pricing of the PLA at $500 would lead to $447 in cost savings per lesion assessed, or $1,341,000,000 in savings based on 3,000,000 surgical biopsies and assuming the test were to be used universally. (19)

SUPPLEMENTAL CLINICAL VALIDATION AGAINST DRIVER MUTATIONS IN MELANOMA

In addition, the PLA has been validated against driver mutations in melanoma (BRAF, NRAS, and TERT Promoter) that are associated with disease progression and histopathologic findings, such as mitotic counts and ulceration. (26-33) In this study, the mutation frequency of these genes was characterized from adhesive patch samples in histopathologically confirmed melanomas (n=30) and non-melanomas (n=73). (25) The frequency of these mutations in the melanoma samples was 77% and statistically higher than the 14% found in non-melanoma samples ($p<<0.00001$). Eighty-six percent (86%) of non-melanomas had no mutations. Adhesive patch mutations were concordant with FFPE tissue samples for the same lesions.

Subsequently, 519 prospectively collected real-world PLA samples were analyzed for these same mutations. Eighty eight percent (88%) of real-world PLA- (negative) test results were negative for any of these melanoma related mutations, similar to the 86% in the validation set. This data confirms the ability of the test to rule out melanoma, or at a minimum, rule out lesions with few mutational risk factors for melanoma. (14). PLA+ (positive) test results had similar mutation frequencies as the validation set and were not statistically different.

CPT CODES

The genes that comprise the PLA test, LINC00518 & PRAME, were subject to review by the CPT editorial panel, the molecular pathology sub-committee (MPAG) and the pathology coding caucus (PCC) during 2017. A total of eight medical societies and groups supported the application, including:

1. American Academy of Dermatology
2. Society for Investigative Dermatology
3. American Society for Clinical Pathology
4. College of American Pathologists
5. American Society of Cytopathology
6. Pathology Coding Caucus
7. Molecular Pathology Advisory Group
8. US and Canadian Academy of Pathology

The LINC00518 & PRAME were each added to the Category 1, Tier 2 molecular CPT code 81401. The changes became effective in January 2018.

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