DermTech

PIGMENTED LESION ASSAY (PLA)

Executive Summary

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. (2) While the purpose of the visual assessment/surgical biopsy 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 (Table 1). This is related to the low specificity of the visual assessment (3%-10%), which results in a high number of biopsies on benign atypical lesions. (3-8) During 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%). (9,10,11) Elmore et al. (2017) concluded that the diagnosis of early stage melanoma was not accurate after finding that 35% of slide interpretations for MIS/Stage 1a melanomas by 187 pathologists received a false negative diagnosis as benign. (10) With the prevalence of early stage melanoma in biopsied lesions at approximately 5%, the negative predictive value ranges from 75%-89%. (7,20) The real NPV of the visual assessment/surgical biopsy pathway is likely in the low to mid 80% range. In a study by Malvehy et al., 206 MIS and Stage 1a (thickness<0.75 mm) melanomas were diagnosed with a sensitivity of 81% and a specificity of 10%. The prevalence of melanoma in the study was 10% yielding an NPV of 83%.

Table 1 compares the key performance metrics of the PLA versus the current pathway (visual assessment and surgical biopsy/histopathology) for managing pigmented lesions. (1-10)

	Current Pathway	PLA
Test Purpose	Rule-out melanoma	Rule-out melanoma
Type	Surgical biopsy/ histopathology	Noninvasive gene expression
NPV	83%	99%
Probability of Missed Melanoma	17%	1%
Number Needed to Biopsy	25	2.7
Number Needed to Excise	5.2	1.6
Cost Per Lesion Tested	$947	$450

This low NPV for the current pathway is accompanied by a high number of unnecessary surgical procedures, again driven by the poor specificity of the visual assessment. (3) 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. (3-8) 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. (12,13,14) 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. (12,13,14) Approximately 5.2 excisions with margins are performed per melanoma identified, emphasizing how the current pathway of surgical biopsy and limited histopathology assessment leads to more complex

and invasive excisions. (12,14) 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. (15,16)

The Pigmented Lesion Assay (PLA) is a gene expression test that helps rule-out melanoma and the need for a surgical biopsy of atypical pigmented lesions. The PLA is based on a new platform technology for non-invasive genomic testing of the skin, which allows the analysis of samples collected from an adhesive patch. 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. (17,18) 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 dramatic reduction in surgical biopsies and subsequent excisions. Consequently, the number of surgical biopsies needed to find one melanoma using the PLA is markedly reduced to 2.7 and the number of excisions needed is reduced to 1.6 (Table 1). (18) Overall, unnecessary surgical procedures are reduced by 88%, which is consistent with a recent (2017) review of 18,715 biopsied pigmented lesions that found that ~90% of biopsies performed on pigmented lesions are negative and unnecessary. (19,20)

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