SKIN

BRIEF ARTICLE

Real-World Performance of a Noninvasive Cutaneous Melanoma Rule-Out Test: A Multicenter U.S. Registry Study

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ABSTRACT

Introduction: Non-invasive adjuncts to visual assessment of pigmented lesions may reduce biopsies of benign lesions without compromising melanoma detection. A non-invasive genomic melanoma rule-out assay analyzes RNA extracted from stratum corneum cells for *PRAME* and *LINC00518*, two genes commonly expressed in melanomas but less often in benign lesions. This study sought to characterize performance of this test in a large patient cohort tested in the real-world clinical setting.
Methods: The test was applied to suspicious pigmented skin lesions at 63 U.S. dermatology and primary care practices. Test results (positive / negative) were compared to pathology diagnoses (melanoma / not melanoma) for lesions that were biopsied and to follow-up visual examination for those that were monitored.
Results: Of 19,653 total lesions evaluated, 17,858 (90.87%) tested negative. Biopsy results and / or follow-up examinations were available for 5,096 lesions, with median and mean follow-up duration of 352 and 341 days, respectively. For melanoma, sensitivity was 95.8% and specificity was 69.4%. Positive predictive value (PPV) was 13.4%, and NPV was 99.7%. For melanoma and 'borderline' lesions combined, sensitivity was 94.2%, specificity was 71.2%, PPV was 20.8%, and NPV was 99.3%.
Conclusion: The results suggest this noninvasive test can facilitate distinction of melanoma from its benign simulators, increasing the proportion of pigmented lesions that can be safely managed with surveillance rather than biopsy and/or excision.

INTRODUCTION

Most skin biopsies performed to rule out melanoma reveal benign lesions, indicating that distinguishing melanoma from its benign simulators by visual examination remains challenging.[1,2] Adjuncts to visual assessment have therefore been sought to reduce biopsies of benign lesions without compromising melanoma detection.[3,4] A noninvasive genomic melanoma rule-out assay that uses adhesive patches to collect cells from the stratum corneum overlying pigmented lesions has been shown facilitate biopsy decision-making.[5] Extracted RNA is

analyzed by RT-qPCR for *PRAME* and *LINC00518*, two genes that are commonly expressed in melanomas but less often in benign lesions.[5] Detection of either or both markers is a positive result and suggests the lesion should undergo biopsy and histopathologic examination for melanoma. Absence of both biomarkers is a negative result and indicates the lesion is usually suitable for surveillance rather than biopsy.[6] This study sought to characterize assay performance of the test in a large patient cohort tested in the real-world clinical setting, with particular focus on negative predictive value (NPV).

METHODS

In this ongoing registry study, the test was applied to suspicious pigmented skin lesions at 63 U.S. dermatology and primary care practices. Test results (positive / negative) were compared to pathology diagnoses (melanoma / not melanoma) for lesions that were biopsied, and to follow-up visual examination for those that were monitored. Since most melanomas have visibly detectable evolution / growth within 3-9 months, monitored lesions were classified as either 'stable / unchanged' or 'changing in a manner concerning for melanoma'. Among biopsied lesions, the proportions diagnosed as melanomas and 'borderline' lesions (probable melanoma or melanoma precursors that are typically managed as potential melanoma, such as dysplastic nevi with severe atypia) were calculated. Statistical analyses were performed using the R software package (version 4.3.1) with 95% confidence intervals calculated using the Clopper-Pearson Exact Binomial Test.

RESULTS

Of 19,653 lesions evaluated, 17,858 (91%) tested negative and 1,795 (9%) tested positive. Biopsy results and / or follow-up examinations were available for 5,096 lesions. Median and mean follow-up duration was 352 and 341 days, respectively. Median patient age was 61 years (18-99) and 58.3% were female. For melanoma, sensitivity was 95.8% and specificity was 69.4%. Positive predictive value (PPV) was 13.4%, and NPV was 99.7%. For melanoma and 'borderline' lesions combined, sensitivity was 94.2%, specificity was 71.2%, PPV was 20.8%, and NPV was 99.3%. Analysis restricted to lesions with at least 6 months follow-up (n=4,461) produced similar or identical point estimates (**Table 1**). Of 240 lesions interpreted by histopathology as melanomas, 230 tested positive and 10 (9 *in situ* and one 0.6mm invasive diagnosed 198 days after testing) tested negative.

DISCUSSION

The primary benefit of this non-invasive melanoma rule-out test is to reduce biopsies of benign lesions that simulate melanoma upon visual assessment. Consistent with prior investigations, more than 90% of suspicious lesions in this study tested negative, suggesting the test can facilitate a substantial reduction in avoidable biopsies.[7] Most test-negative lesions remained stable / unchanged throughout the course of the study (median and mean follow-up of 352 and 341 days, respectively), confirming prior observations that negative lesions are typically safe to monitor rather than biopsy.[7,8]

The test ruled out melanoma and borderline lesions typically managed as melanoma with an NPV of >99%. NPV point estimates were associated with narrow 95% confidence intervals. NPV is generally considered the critical performance metric for a rule-out test

Table 1. Test performance in lesions with biopsy or follow-up of any duration (n=5,096) and those with biopsy or at least 6 months of follow-up (n=4,461). The 95% confidence intervals for sensitivity, specificity, PPV and NPV are in parentheses.

	Lesions with Biopsy / Follow-Up of Any Duration (n=5,096)		Lesions with Biopsy / ≥6 Months Follow-Up (n=4,461)	
	Melanoma	Melanoma + Borderline	Melanoma	Melanoma + Borderline
Sensitivity	95.8% (92.5% - 98.0%)	94.2% (91.3% - 96.3%)	95.8% (92.5% - 98.0%)	94.2% (91.3% - 96.3%)
Specificity	69.4% (68.1% - 70.7%)	71.2% (69.9% - 72.5%)	65.0% (63.5% - 66.4%)	66.9% (65.5% -68.4%)
PPV	13.4% (11.8% - 15.1%)	20.8% (18.9% - 22.8%)	13.5% (11.9% - 15.2%)	20.9% (19.0% - 22.9%)
NPV	99.7% (99.5% - 99.9%)	99.3% (99.0% - 99.6%)	99.6% (99.3% - 99.8%)	99.2% (98.8% - 99.5%)

since a negative result is often used to defer further testing in favor of surveillance.

The positive predictive value (PPV) was 13%. This compares favorably to the current standard of visual assessment with or without dermoscopy, which has a PPV of approximately 4%.[1]

Strengths of the study include the real-world setting, duration of follow-up, and large cohort size. Limitations include a cohort comprised of individuals evaluated primarily by dermatologists, which may not represent the general population, and comparison to histopathologic diagnosis in biopsied lesions, which has lower accuracy for early-stage melanocytic neoplasms.[9] The results suggest this noninvasive test can facilitate distinction of melanoma from its benign simulators, increasing the proportion of pigmented lesions that can be safely managed with surveillance rather than biopsy and/or excision and providing better health outcomes for patients.

Conflict of Interest Disclosures: MDK, MKS, LKF and MW are consultants and / or investigators of DermTech; AR, BJ, and LEC are employees of DermTech.

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