A Non-invasive 2-Gene Molecular Assay Shows Promise in Assessment of Pigmented Lesions

More studies are needed, but a non-invasive assay that identified melanoma gene expression could support clinical decision making.

BY JONATHAN WOLFE, MD

While dermatologists are adept at distinguishing frankly benign from malignant lesions on visualization, the larger challenge is in determining which lesions of dubious nature should be biopsied and which can be followed. Histopathologic diagnosis of a biopsy sample remains the cornerstone of skin cancer diagnosis, as described in the AAD’s current Guidelines of Care for Melanoma.1

The first step for a definitive diagnosis of cancer is a biopsy that may occur by removing part of the lesion (incisional biopsy) or the entire lesion (excisional biopsy). For a lesion clinically suspicious for cutaneous melanoma, one should ideally perform a narrow excisional biopsy that encompasses the entire breadth of the lesion with clinically negative margins to a depth sufficient to ensure that the lesion is not transected. It has been suggested that 1- to 3-mm margins are required to clear the subclinical component of most atypical melanocytic lesions.

Biopsy, while essential to a firm diagnosis, is not without risks, including scarring and infection. These risks tend to be minimal and readily managed, but dermatologists and their patients would generally prefer to minimize unnecessary biopsies and thereby eliminate risks.

With time, dermatologists become adept at identifying suspicious lesions, and we devise our own individual thresholds for biopsy based on the appearance and characteristics of the lesion, its anatomic location, patient reported symptoms, patient history, and other key considerations. These thresholds are not absolute. Tools like dermoscopy give us additional information to support the decision to biopsy or watch a lesion. And in each clinical encounter we weight certain “external” factors that may also influence our course of management. A patient who has proven non-adherent with follow-up screens or an elderly patient with early dementia who cannot be relied upon to monitor a lesion may tip the balance toward biopsy where another patient with a similar lesion would not.

Without fail, we will encounter lesions that fall right at the threshold, with no compelling evidence to support a biopsy or a watch. In most cases, we likely err on the side of doing the biopsy “to be safe.” For a lesion on the trunk or the upper arm, this may be of little consequence to the patient. But what about biopsies in anatomically sensitive areas, like the face? If we could avoid unnecessary biopsies in such areas, we would.

Researchers and developers have been working together to create imaging/scanning devices that would support clinical decision making regarding biopsy and help to identify lesions likely to be melanomas. While some of these devices have shown promise, they are potentially costly to acquire and are not typically covered by third-party insurance. Therefore, patient access is limited.

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Additionally, these imaging devices are assessing lesions based on the same sort of data the dermatologist is using. They are largely based on based on measuring light scattering and absorption properties of the lesions—albeit at a dif-
ferent level than can be visualized with the naked eye. All in all, the supportive information/evidence that these devices provide has not been shown to substantially alter physician behaviors. A dermatologist leaning in favor of biopsy is unlikely to rely on a digital imaging system to deter such a decision. Therefore, such devices largely serve to increase the dermatologist’s level of confidence in the decision to biopsy.

But what if there were a non-invasive, easily accessible, and effective tool for assessing lesions in the clinic based on objective criteria, such as gene expression in the lesion? Such an approach would provide different biological information to the dermatologist to augment visual assessment. New data suggest that use of a non-invasive pigmented lesion assay (PLA) for detecting LINC00518/PRAME expression could, indeed, confer clinical benefit in directing the dermatologist’s decision to biopsy suspicious lesions.

Previous research has shown that the two-gene PLA to detect expression of LINC00518 (long intergenic non-protein coding RNA 518) and PRAME (preferentially expressed antigen of melanoma) enabled classification of pigmented lesions clinically suspicious of melanoma with a sensitivity of 91 percent and specificity of 69 percent, which authors said “compares favorably to the 85%-87% level from histopathologic assessments after surgical biopsies.”

This two-gene PLA differs from other molecular tools that have focused on detecting mutations in melanoma-related genes such as BRAF and NRAS or KIT. The non-invasive, two-gene assay detects RNA transcripts of LINC and PRAME in skin samples collected through an adhesive patch-based Class I biopsy device.

**CLINICAL ASSESSMENT**

The clinical benefit and utility of the assay were assessed in a study involving 45 dermatologists who evaluated 60 clinical and dermoscopic images of clinically atypical pigmented lesions in two rounds. Eight of the lesions were histopathologically confirmed melanomas; 52 were non-melanomas. Participating reviewers were blinded to the confirmed diagnoses.

On initial review of the lesions (Round A), dermatologists were provided patient information, such as personal or family history of melanoma or other skin cancers, sex, race, and age, Fitzpatrick skin type, and lesions location. Characteristics (new, changing) or “symptoms” (itching, oozing) associated with the lesion, were also provided.

On invitation and before Round B, participating dermatologists were provided information about the nature and performance characteristics of the PLA. In Round B, the same lesions were reviewed, however, molecular pathologic PLA test report containing gene expression results for each lesion was provided. A “positive” test result is provided if LINC00518 and/or PRAME are detected, which is consistent with a gene expression signature seen in more than 90 percent of melanomas.

An algorithmic PLA score was also provided, based on a scale of 0 to 100. The authors note that the median PLA scores were 78 for invasive melanoma and melanomas in situ, 41 for atypical nevi, five for conventional nevi, and 16 for other nonmelanoma pigmented lesions.

Based on PLA results, reviewers reduced the decision to biopsy by 581 out of 2,340. The mean biopsy specificity increased from 32.1 percent without the test to 56.9 percent when the PLA result was considered. There was a statistically significant change in readers’ mean specificity pre- and post-PLA. Mean biopsy sensitivity without PLA was 95 percent. This increased significantly to 98.6 percent post-PLA.

In both Round A and Round B, dermatologists were asked to rate their confidence in their decision to biopsy or not biopsy based on a 5-point Likert scale. While mean overall confidence score changed from 3.1 to 3.3 using PLA, the mean confidence scores for malignant lesions increased from 3.6 to 4.3.

**IMPLICATIONS**

The potential to support clinical decision making to biopsy a lesion using a non-invasive, accessible, in-office patch is intriguing. The utility of such an approach is obvious in its ability to potentially reduce the cost of unnecessary biopsies and the risks for scarring and other adverse events.

There are some limitations to the PLA discussed here. It does not work on the mucous membranes, the palms of hands, the soles or feet, or nails. In other words, it is not useful in some of the areas where patients and dermatologists would most like to avoid unnecessary cuts for functional or aesthetic reasons. The PLA also is not for use on ulcerated or bleeding lesions, but these are strong indications of a need to biopsy, anyway.

Further study would be welcome, and we look forward to accumulated clinical experience. However, early data are promising, and dermatologists can be optimistic about a possible new tool in the effort to identify and treat melanoma as early as possible.

Jonathan Wolfe, MD is an Associate Professor of Dermatology at the University of Pennsylvania.