A Non-invasive Technique for Detecting Melanoma

By Danielle Ruppenthal, MPAS, PA-C, and Mark Hyde, PhD, PA-C

ABSTRACT

Advances in genomic technology have allowed providers to evaluate pigmented lesions with greater reliability. Using all available methods to evaluate changing lesions has led to earlier detection and actionable results.

KEYWORDS

Atypical pigmented lesions, genomic technology

TAKE-HOME POINTS:

- Improve understanding of available pre-biopsy genomic testing options
- Understand how genomics can complement the traditional visual assessment pathway
- Share personal experience to illustrate the impact of genomics in pigmented lesion assessment

INTRODUCTION

New genomic technology in dermatology is creating thorough and less invasive methods to evaluate pigmented lesions and melanoma. Using these methods, providers are able to test appropriate lesions with greater reliability. This has the potential for earlier detection of disease and actionable results. One method uses a non-invasive adhesive patch to collect epithelial cells and test for genomic abnormalities within pigmented lesions. Other tests are also available to evaluate for genomic changes after biopsy to aid in diagnosis and prognosis.[1] We now have the means to test atypical pigmented lesions that are clinically indeterminate or are in a location that makes a biopsy difficult.

There are several ways to get information about an atypical pigmented lesion. Traditional biopsies include shave, punch, incisional, and excisional. Confocal microscopy has been developed to test lesions by an imaging technique that is non-invasive but still relies on subjective decision making. Cutting-edge technology can now look at deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) to assess the biologic potential of skin lesions. To differentiate, genetics are used to look at one gene to assess for a mutation and associated risks. Genomics assess the genome (multiple genes/expression of genes and interactions) to find additional, clinically useful information and associated risks.[2]

The DermTech Melanoma Test (DTMT [DermTech, La Jolla, California]) is comprised of two assays: the Pigmented Lesion Assay (PLA) and the Telomerase Reverse Transcriptase (TERT) Add-on assay. The PLA detects two RNA biomarkers—preferentially expressed antigen in melanoma (PRAME) and long intergenic non-protein coding RNA 518 (LINC00518). The TERT add-on assay detects DNA TERT promoter mutations and is only run following PLA testing when ordered and if sufficient genomic material is available.

The PLA harvests epithelial cells non-invasively through an a non-invasive adhesive patch and uses real-time quantitative polymerase chain reaction (qPCR) to identify PRAME and LINC00518. The same method of collecting cells with a SmartSticker is used for the more recent TERT add-on assay. Providers can order Adhesive Skin Collection Kits from their local representative or directly through the company.

Non-invasive epidermal genomic testing can assess the surface of the entire lesion. Conversely, traditional histopathologic sections can only assess a small percentage of the lesion. Both LINC00518 and PRAME are commonly detected in melanoma and have a role in oncogenesis. TERT mutations, detected by the TERT add-on assay, while not specific to melanoma, have been correlated with more aggressive tumor behavior. The absence of these three markers is associated with a negative predictive value greater than 99.5 percent, and also has a high sensitivity of 91 to 97 percent.[3,4]

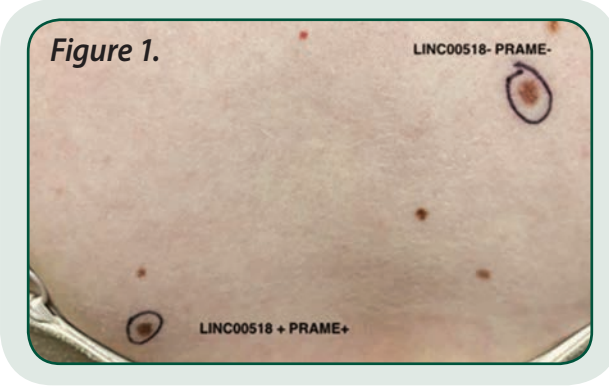
We present the following case to illustrate how non-invasive genomic testing can be integrated into the current pathway for screening and treatment of pigmented lesions.

CASE DESCRIPTION

A 29-year-old female patient presented to the clinic for evaluation of nevi. The patient had no family history of melanoma. She had a history of a single moderately dysplastic nevus three years prior to presentation. She was not concerned with any specific lesions nor aware of any changes in her lesions. Her exam showed several nevi violating ABCDE (Asymmetry, Border, Color, Diameter, Evolving) criteria, primarily larger than 6 mm. The patient was interested in avoiding scars and unnecessary biopsies.

Non-invasive epidermal genomic testing was discussed and questions about the technology and accuracy were answered. The patient opted for the non-invasive test to determine which lesions needed traditional histologic evaluation. Seven nevi were considered

clinically indeterminate and tested using the DTMT. Six of seven lesions considered clinically indeterminate showed no genomic aberrations. One nevus on the left mid-back expressed the genomic RNA markers LINC00518 and PRAME by real time qPCR. Due to the negative predictive value >99 percent, the patient was reassured about the six genomically stable lesions. The lesion that expressed LINC00518 and PRAME was removed with minimal margins in an effort to evaluate the entire depth and breadth. Upon histopathologic evaluation the lesion was determined to be melanoma in-situ (MIS) *(Figure 1)*. This was excised with 0.7 cm margins and confirmed to have clear margins.



A history of a moderately dysplastic nevus and MIS increased this patient's risk for future melanoma, and she was therefore placed on a more frequent follow-up schedule. At her follow-up visit (7 months after the initial diagnosis of MIS), the patient was found to have six additional clinically indeterminate lesions that violated at least one of the ABCDE criteria. At that appointment, the DTMT was again used. Three of these lesions showed no genomic atypia. Two lesions were positive for LINC00518 and PRAME and one lesion positive for PRAME. Again, the lesions which showed genomic aberrations were removed in an effort to evaluate the entire depth and breadth. One was again diagnosed as MIS, one was a moderately dysplastic nevus, and one a severely dysplastic nevus (SDN). The MIS and SDN were appropriately excised to obtain clear margins.

With a history of two MIS and multiple dysplastic nevi, this patient has continued to be monitored by a team of dermatology providers. Because none of the lesions that tested positive were of high clinical concern, the patient and providers have adopted a lower threshold for testing, both genomic/non-invasive and traditional sampling methods. This case demonstrates how non-invasive genomic testing assists in triaging lesions that are clinically indeterminate or may not qualify for a traditional biopsy. In this case, two MIS and one SDN were found that might otherwise have been diagnosed later or missed. It is also worth noting that the use of genomic testing prevented the invasive sampling of benign lesions. In other words, only 1 of 4 lesions biopsied or 25 percent was found to be a benign lesion while 3 of 4, or 75 percent, of biopsied lesions were found to be MIS or SDN. As recommended, the patient has continued to follow up regularly. None of the lesions considered low risk by genomic testing have changed or exhibited any other clinical signs of atypia.

Commentary from Author/Patient: Danielle Ruppenthal, MPAS, PA-C

This case is personal to me as I am the patient in the case described and a dermatology provider. This experience has led to more compassion and empathy for my patients as well as an increased interest in genomic abnormalities in dermatology. Identifying cancers early, like in my case, invariably saves lives. If my colleagues had waited to test my lesions until a more visible physiologic change occurred, the prognosis could have been different. Now, when examining atypical pigmented lesions, I take advantage of multiple different modalities, including biopsy, dermoscopy, confocal microscopy, and the DTMT to improve my accuracy. This allows a wide variety of lesions to be evaluated visually and biologically with less morbidity. Patients are made aware of options before testing and appropriately play a role in the medical decision-making process. This not only improves my clinical acumen but also increases my patients' confidence and comfort. Having multiple options and understanding and utilizing the advances in testing saves lives, including mine.

REFERENCES

1. Greenhaw BN, Covington KR, Kurley SJ, et al. Molecular risk prediction in cutaneous melanoma: A meta-analysis of the 31-gene expression profile prognostic test in 1,479 patients. J Am Acad Dermatol. 2020 Sep;83(3):745-753. doi: 10.1016/j.jaad.2020.03.053. Epub 2020 Mar 27. PMID: 32229276.
2. Ferris LK, Jansen B, Ho J, et al. Utility of a noninvasive 2-gene molecular assay for cutaneous melanoma and effect on the decision to biopsy. JAMA Dermatol 2017; 153: 675–80. DOI: 10.1001/jamadermatol.2017.0473.
3. Gerami P, Yao Z, Polsky D, et al. Development and validation of a noninvasive 2-gene molecular assay for cutaneous melanoma. J Am Acad Dermatol. 2017;76(1):114-120.e2. doi:10.1016/j.jaad.2016.07.038
4. Ferris L, Jansen B, Yao Z, et al. Real-world experience and clinical utility of a non-invasive gene expression test for primary cutaneous melanoma and validation against high risk driver muations in BRAF, NRAS and the TERT promoter. Presented at: International Investigative Dermatology Meeting, Late Breaking Abstract. Orlando, FL. May 16-19, 2018.

Authorship statement: *Danielle Ruppenthal wrote the manuscript and Mark Hyde provided editorial advice and some writing.*

Danielle Ruppenthal, MPAS, PA-C, *is from Bopp Dermatology and Facial Plastic Surgery, in Metairie Louisiana.*

Mark Hyde, PhD, PA-C, *is Area Medical Director - West for DermTech, La Jolla, California*

Disclosures: *Danielle Ruppenthal, MPAS, PA-C, is on the speaker bureau for DermTech (La Jolla, California) and speaker bureau and advisory board for Castle Biosciences (Friendswood, Texas). Mark Hyde, PhD, PA-C, is an employee of and holds stock in DermTech.*