VIEWPOINT

Gene Expression Profile Testing for Thin Melanoma
Evidence to Support Clinical Use Remains Thin

Carrie L. Kovarik, MD
Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia.

Emily Y. Chu, MD, PhD
Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia.

Adewole S. Adamson, MD, MPP
Department of Internal Medicine, Dell Medical School, The University of Texas at Austin; and LIVESTRONG Cancer Institutes, The University of Texas at Austin.

Corresponding Author: Carrie L. Kovarik, MD, Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, 3600 Spruce St, Two Maloney Building, Philadelphia, PA 19104 (carrie.kovarik@pennmedicine.upenn.edu).

Cutaneous melanoma incidence in the US is increasing, with an estimated 96 480 cases in 2019 compared with 47 700 in 2000 (https://seer.cancer.gov). Most cutaneous melanomas are limited to the skin (84%), defined as stage I or II disease by the American Joint Committee on Cancer.[1] For all stages combined, 5-year mortality rate is 7.8%, but mortality is more likely when cutaneous melanoma has metastasized to lymph nodes or organs (stage III or IV).[1]

Thin melanomas, defined here as thickness of 1.0 mm or less (T1), include T1a (<0.8 mm thick, no ulceration) and T1b tumors (<0.8 mm thick with ulceration or 0.8-1.0 mm thick with or without ulceration); together they constitute approximately 70% of cutaneous melanomas.[1] Recommended treatment for both T1a and T1b tumors, according to National Comprehensive Cancer Network (NCCN) guidelines, is wide local excision. Sentinel lymph node (SLN) metastases at the time of melanoma diagnosis are more common in T1b disease (5%-10%) compared with T1a disease (<5%).[1,2] For that reason, NCCN guidelines recommend considering SLN biopsy (SLNB) only for T1b melanomas or for T1a melanomas with adverse features (high mitotic index, ≥2 mitoses/mm^2 [particularly in patients younger than 40 years old]; lymphovascular invasion; or a combination of these factors).[1,3] Although studies have provided guidance, the decision to proceed with SLNB in thin melanomas is not clear cut. If a noninvasive test could identify patients at high risk for metastasis, leading to a management plan that improved outcomes, then lives could be saved.

A proprietary 31-gene expression profile (GEP) assay (Castle Biosciences) has been developed in an attempt to address this clinical dilemma. This assay uses quantitative reverse transcriptase–polymerase chain reaction techniques on RNA extracted from formalin-fixed, paraffin-embedded biopsy specimens to determine expression levels of reported genes associated with melanoma metastasis. Gene expression levels are used to stratify patients according to risk of future metastatic disease, with class 1A having lowest risk, class 1B/2A having intermediate risk, and class 2B having high risk. According to company-set parameters, patients with stage I/II disease have 5-year distant metastasis–free survival (DMFS) rates of 97% and 65% for class 1A and 2B, respectively. The ultimate goals are to help clinicians use risk categories to (1) determine whether to perform SLNB and (2) consider the intensity of follow-up, referrals, and imaging. Assessing the clinical utility of 31-GEP testing requires rigorous evaluation of whether the test accomplishes those goals, as well as consideration of disadvantages.

The majority of published studies evaluating 31-GEP testing have been retrospective studies or prospective cohort studies without a comparator group.[4] In one study, 281 patients with T1 melanoma were included, and the majority (89.3%) were class 1. Of the 10.7% of patients deemed class 2, 5.3% were class 2B (high risk).[5] Patients with T1 tumors classified as class 2B had a 5-year DMFS rate of 84.4% (95% CI, 66.6%-100.0%), whereas in class 1A, DMFS was 97.2% (95% CI, 95.1%-99.4%). The wide CI for class 2B denotes the uncertainty of 31-GEP prediction. Using these data, Marchetti et al[6] modeled test characteristics in T1 melanomas and showed that 31-GEP testing has a sensitivity of 21% and specificity of 90% for DMFS. Positive predictive value for 31-GEP in this model is 10%, and only 1% of patients would gain correct information about being at high risk for metastasis despite having thin melanoma.[6] An incorrect result would be given to 13% (false positives or false negatives), leading to false assurance or unjustified testing.[6] When the 31-GEP assay and class risk categories were developed, training and validation data included very few metastases from T1 melanomas (9% and 3%, respectively), which may be reflected in the low sensitivity in this population.[4]

Overall prognosis for thin melanoma is good, with melanoma-specific survival rates of 98% and 94% at 10 years for T1a and T1b melanomas, according to the American Joint Committee on Cancer; however, some patients develop regional metastasis, which classically occurs after a protracted period, sometimes decades after initial diagnosis. The incidence of thin melanomas is increasing, and it is important to identify those at highest risk for poor outcome.[1] Numerous studies have identified risk factors that may be predictive of positive SLN in thin melanoma, such as ulceration, high mitotic rate, and younger patient age. These risk factors are easily determined and inexpensive, and given the strength of evidence, some are now referred to as adverse features by NCCN guidelines for use in clinical staging and workup.[1]

A good predictive test is evaluated in phases to determine whether it adds information to established risk markers, improves clinical outcomes, and reclassifies patients into prognostic groups for clinical management. Unlike the 31-GEP assay in cutaneous melanoma, GEP testing in early-stage breast cancer has been validated in randomized clinical trials and improves clinical decision-making for therapy.[7] One trial investigated whether GEP testing would enable reduction in chemotherapy by determining whether patients with clinically high-risk disease but a low-risk GEP score have a 5-year DMFS greater than 92%, which is the cutoff for benefit from chemotherapy. Patients were randomized to adjuvant chemotherapy or no chemotherapy. Results showed that 5-year

DMFS was 94.7% in patients not receiving chemotherapy. NCCN and American Society of Clinical Oncology guidelines have incorporated GEP testing based on clinical evidence.

Currently, there are no 31-GEP studies that stratify patients with melanoma according to clinical groups and genomic risk and then randomize patients to an intervention, similar to the breast cancer study. However, one cohort study[8] evaluated whether the 31-GEP assay could identify patients with low risk for SLN positivity in T1/T2 melanomas who would be considered for SLNB based on guidelines. The results suggest that patients 65 years or older and with class 1A GEP risk have a 1.6% SLN positive rate and therefore may be able to avoid the procedure. This is a promising direction of investigation for use of 31-GEP testing in a narrow, defined population, and further randomized studies with outcomes data are needed to establish clinical utility.

The 31-GEP risk stratification is also meant to guide follow-up care for melanoma. There is currently no evidence that demonstrates that a change in surveillance practices based on 31-GEP risk positively influences outcomes; therefore, it may be difficult for clinicians to determine the clinical action that should follow a result. However, publications have encouraged changes in diagnostic and management protocols based on 31-GEP testing results.[6] These recommendations include use of 31-GEP in any patient with melanoma with negative SLNB, as well as patients with T1 tumors (including tumors with a depth ≤0.3 mm with adverse features) for SLNB decision guidance.[6,9] A recent study surveyed 181 dermatology clinicians (approximately 50% dermatologists practicing for more than 20 years) and found that 22% of clinicians would order 31-GEP testing on nonulcerated melanomas with a Breslow depth of 0.26 mm, and 78% would order testing on tumors with a depth of 0.50 mm.[4] Neither NCCN nor American Academy of Dermatology guidelines include 31-GEP testing as part of routine care for any melanoma.[1,3]

Another important consequence of routine use of 31-GEP is cost. Despite the test not being cleared by the US Food and Drug Administration (FDA), private insurance and Medicare have started to reimburse for 31-GEP testing in certain cases. FDA clearance is currently not required for laboratory-directed tests, such as GEP. However, companies may opt to submit some laboratory-directed tests to undergo parallel FDA/Centers for Medicare & Medicaid Services review for approval, given this signifies assurance of safety, effectiveness, and clinical validity. Ongoing Medicare coverage, at $7193 per test (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Downloads/List-of-Approved-ADLTs.pdf), will be contingent upon demonstrating (1) 95% or greater DMFS/melanoma-specific survival at 3 years in patients who forgo SLNB and (2) higher SLN positivity in patients selected for SLNB by 31-GEP testing vs standard of care. This contingency is owing to low strength/weight of evidence determined by Centers for Medicare & Medicaid Services.[10] Given that 31-GEP testing is being used in thin melanoma, health care spending owing to potential high-volume use and subsequent disease surveillance could be substantial, with unknown benefit and undetermined cost-effectiveness.

Until we have clear evidence that 31-GEP results affect patient outcomes, we should not use it to influence care decisions in patients with thin melanoma. Breast cancer GEP testing is FDA approved and incorporated into NCCN and American Society of Clinical Oncology guidelines based on well-executed prospective studies, and we should expect the same standards in dermatology. For a potentially devastating disease such as melanoma, a proven test that guides management would be welcome; however, current evidence for 31-GEP use in thin melanomas remains thin.

ARTICLE INFORMATION

Published Online: April 15, 2020. doi:10.1001/jamadermatol.2020.0894

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Coit DG, Thompson JA, Algazi A, et al. Melanoma, version 2.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14(4):450-473. doi:10.6004/jnccn.2016.0051

2. Andtbacka RH, Gershenwald JE. Role of sentinel lymph node biopsy in patients with thin melanoma. *J Natl Compr Canc Netw*. 2009;7(3):308-317. doi:10.6004/jnccn.2009.0023

3. Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol*. 2019;80(1):208-250. doi:10.1016/j.jaad.2018.08.055

4. Berman B, Ceilley R, Cockerell C, et al. Appropriate use criteria for the integration of diagnostic and prognostic gene expression profile assays into the management of cutaneous malignant melanoma: an expert panel consensus-based modified Delphi process assessment. *Skin (Los Angeles)*. 2019;3(5):291-306. doi:10.25251/skin.3.5.1

5. Gastman BR, Gerami P, Kurley SJ, Cook RW, Leachman S, Vetto JT. Identification of patients at risk of metastasis using a prognostic 31-gene expression profile in subpopulations of melanoma patients with favorable outcomes by standard criteria. *J Am Acad Dermatol*. 2019;80(1):149-157.e4. doi:10.1016/j.jaad.2018.07.028

6. Marchetti MA, Bartlett EK, Dusza SW, Bichakjian CK. Use of a prognostic gene expression profile test for T1 cutaneous melanoma: will it help or harm patients? *J Am Acad Dermatol*. 2019;80(6):e161-e162. doi:10.1016/j.jaad.2018.11.063

7. Cardoso F, van't Veer LJ, Bogaerts J, et al; MINDACT Investigators. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375(8):717-729. doi:10.1056/NEJMoa1602253

8. Vetto JT, Hsueh EC, Gastman BR, et al. Guidance of sentinel lymph node biopsy decisions in patients with T1-T2 melanoma using gene expression profiling. *Future Oncol*. 2019;15(11):1207-1217. doi:10.2217/fon-2018-0912

9. Marks E, Caruso HG, Kurley SJ, et al. Establishing an evidence-based decision point for clinical use of the 31-gene expression profile test in cutaneous melanoma. *Skin*. 2019;3(4):239-249. doi:10.25251/skin.3.4.2

10. Centers for Medicare & Medicaid Services. Local coverage determination (LCD): MolDX: DecisionDx-Melanoma (L37725) [date in effect: February 3, 2020]. Accessed February 3, 2020. https://www.cms.gov/medicare-coverage-database/