Response to: "Use of a prognostic gene expression profile test for T1 cutaneous melanoma: Will it help or harm patients?"

To the Editor: Improved risk prediction for thin melanoma (T1 tumor; thickness, ≤1.0 mm) is critical, given the substantial number of patients with tumors initially diagnosed as T1 who contribute to disease-specific mortality.[1] A challenge in melanoma care is determining management of the patient with low-stage disease. Multidisciplinary care is provided to patients with higher-stage disease, but thin tumors, for the most part, receive only dermatologic follow-up. The burden of the rare patient with a T1 tumor who has metastasis may fall solely to the responsibility of individuals who are not focused on cancer care. Thus, despite advances in American Joint Committee on Cancer staging, additional independent prognostic information is important to the patient with melanoma and the physician who may request assistance when providing care. Like current staging factors, the 31-gene expression profile test (31-GEP) may be imperfect in teasing out rare thin tumors that are at risk of metastasis, but the test does provide clinically impactful risk prediction.

Marchetti et al have suggested that patients with nonmetastatic class 2 tumors would be "harmed by an incorrect result" of the 31-GEP.[2] Even with a noted false-positive rate, having a target cohort comprising the majority of patients who will fail surgical therapy provides a rationale to increase surveillance and multidisciplinary care. There are several potential explanations for why patients with T1 tumors with high-risk biology do not develop metastasis, including curative surgical intervention and an efficacious host immune response. The definition of *harm* should also be considered in the context of other interventions that are routinely utilized in melanoma. For example, sentinel lymph node–positive patients can receive adjuvant therapy associated with serious and sometimes irreversible toxicities, despite having a good prognosis (ie, a 93% 5-year melanoma-specific survival rate for stage IIIA disease).

Marchetti et al[2] have also speculated that "86% of patients would be unaffected" by a test result that aligns with American Joint Committee on Cancer–determined risk. Previous studies have shown that a 31-GEP class 1 result provides reassurance of a low-risk tumor, leading to reduced intensity of patient follow-up and referral patterns.[3-5] One could argue that patients who have a negative sentinel lymph node biopsy result but experience metastasis are also harmed by an incorrect result; notably, these patients constitute the majority of those who die of melanoma.[6]

In their model for 31-GEP clinical value based on test accuracy metrics, Marchetti et al[2] have not only overestimated the incidence of a class 2 result in T1 tumors but have also failed to account for the 31-GEP subclasses 1A (lowest risk), 1B, 2A, and 2B (highest risk). Distinguishing class 1A tumors with a higher than 95% negative predictive value (99% in Greenhaw et al[3]) and class 2B tumors with a 40% positive predictive value for recurrence is impactful for patients.[4,5]

Clinicopathologic features do not identify all thin melanomas that will recur. The multivariate analysis described in Gastman et al[7] (Supplementary Table III [available at http://www.jaad.org]) emphasizes the value of molecular subclassification in the context of these factors; the 31-GEP class 2B result was the only feature independently associated with recurrence risk for T1 tumors. On the basis of statistical and clinical evidence, the 31-GEP test offers valuable and actionable information to patients with thin melanoma.

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