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

To the Editor: Gastman et al have reported the performance of a 31-gene expression profile test (31-GEP) in predicting the metastatic risk of patients with melanoma who are at low absolute risk of recurrence, including those with T1 (thickness, ≤1 mm) tumors.[1] As T1 melanomas account for at least 70% of melanoma cases in the United States,[2] the findings of Gastman et al[1] have significant potential public health relevance.

Among 281 patients with T1 melanoma, 14 (5.0%) had a distant metastasis. Gastman et al[1] found a difference in 5-year distant metastasis–free survival (DMFS) in patients with T1 melanoma with class 1 and class 2 scores, respectively. However, the poor diagnostic accuracy of the test is likely to limit its clinical utility in these patients.

From the data presented in Supplemental Fig 1 of the article by Gastman et al,[1] the sensitivity, specificity, positive predictive value, and negative predictive value of a class 2 score in predicting DMFS among T1 melanomas were 21%, 90%, 10%, and 96%, respectively. To examine the potential clinical impact of the test, consider the results of 100 hypothetical patients with T1 melanomas with a 5-year DMFS of 95% (Fig 1). After application of the described statistical parameters of the test, 86% of

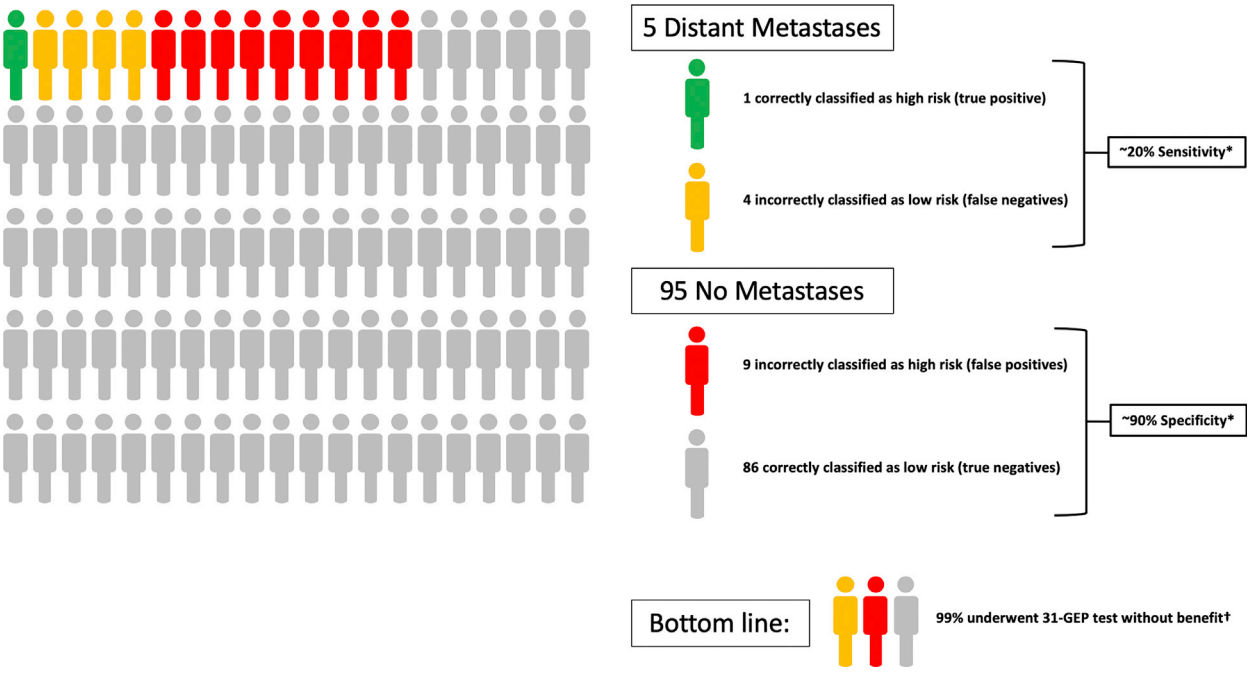

Fig 1. Estimate of the clinical performance of the 31-gene expression profile test with 100 hypothetical patients with T1 (thickness, ≤1 mm) cutaneous melanoma and a 5-year distant metastasis–free survival rate of 95%. *These data assume a 5-year distant metastasis–free survival rate of 95% and 31-gene expression profile test sensitivity and specificity of approximately 20% and approximately 90%, respectively.[1] Therefore, there would be 10 class 2 results (9 false positives and 1 true positive) and 90 class 1 results (4 false negatives and 86 true negatives). †As the baseline risk of distant metastasis is approximately 95% and the class 1 risk of distant metastasis is approximately 96%, the negative predictive value of the test is unlikely to benefit patients or alter physician-directed surveillance. Comparable analyses were performed for recurrence-free survival (RFS), which was defined by Gastman et al[1] as time from diagnosis to local, regional, or distant recurrence. From the data presented in Supplemental Fig 1 of the article by Gastman et al,[1] the sensitivity, specificity, positive predictive value, and negative predictive value of a class 2 score in predicting 5-year RFS among patients with T1 melanomas were 33%, 91%, 20%, and 95%, respectively.[1] If the 31-gene expression profile test was applied to 100 hypothetical patients with T1 melanoma and a 5-year RFS rate of 94%,[1] there would be 2 true positives, 9 false positives, 4 false negatives, and 85 true negatives; thus, 85% of patients would be unaffected, 13% could be harmed by an incorrect result, and 2% could potentially benefit from a correctly anticipated local, regional, or distant recurrence.

patients would be unaffected, 13% could be harmed by an incorrect result, and 1% could potentially benefit from a correctly anticipated distant metastasis.

It remains speculative, however, that the 1% of true positives would benefit from testing, considering that (1) even with intensive imaging protocols, approximately 40% of patients' recurrences are first identified symptomatically or by physical examination by a physician[3]; (2) the magnitude, if any, of treatment benefit from screen versus symptomatic detection of metastatic disease is unknown; and (3) there are no data to support the pre-emptive use of adjuvant treatment in patients with a 10% or lower 5-year risk of distant metastasis.

The clinical futility of the 31-GEP test in low-risk, thin melanomas is further supported by data published by Greenhaw et al.[4] They tested 219 patients with stage 1 melanoma who had a 5-year metastasis-free survival rate of 99.5%; there were 201 class 1 scores and 18 class 2 scores. As the only metastasis occurred in a patient with a class 1 score, the test achieved a sensitivity of 0% and specificity of 92%. Overall, none of their patients with stage 1 disease appeared to benefit from 31-GEP testing, but 8% (n = 18) were potentially harmed by being incorrectly identified as being at high risk of metastasis.

Before a prognostic test for cutaneous melanoma is embraced, the test must be demonstrated to be valid and clinically useful in prospective studies with predetermined end points. Several studies over the past few years have portrayed the 31-GEP test as having analytic and clinical validity, but the clinical utility and cost-effectiveness of the test remain unproved, especially in patients at low risk of metastasis or death. In our opinion, the data provided by Gastman et al[1] and Greenhaw et al[4] provide compelling evidence against routine clinical use of the 31-GEP test for T1 melanomas. Its indiscriminate use in the United States has the potential to incorrectly risk-stratify more than 8000 individuals/y with no demonstrable benefit.

Michael A. Marchetti, MD,[a] Edmund K. Bartlett, MD,[b] Stephen W. Dusza, DrPH,[a] and Christopher K. Bichakjian, MD[c]

From the Dermatology Service, Department of Medicine,[a] and Gastric and Mixed Tumor Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York,[b] and Department of Dermatology, University of Michigan Health System, Ann Arbor, Michigan[c]

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Reprint requests: Michael A. Marchetti, MD, Memorial Sloan Kettering Cancer Center, Medicine, Dermatology Service, 16 E. 60th St, New York, NY 10022

E-mail: marchetm@mskcc.org

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