Problematic methodology in a systematic review and meta-analysis of DecisionDx-Melanoma

To the Editor: Greenhaw et al[1] conducted a meta-analysis of the prognostic effect size of the 31-gene expression profile test and concluded that it "… [has] an evidence rank of level 1A under the SORT and Oxford systems." However, methodologic shortcomings[2] and the small sample size of studies[3] suggest that the estimated 31-gene expression profile effect size is unlikely to be an accurate measure of the true effect size.

Lack of a prespecified protocol: A protocol allows identification of selective reporting, permits examination of planned methods, and prevents arbitrary inclusion and exclusion of data.[4] For example, the rationales for (1) the exclusion of nonoverlapping patients reported by Keller et al[5] and (2) the inclusion of the internal validation cohort[6] are unclear, particularly when individual patient data were available.

Adjustment for confounders and missing data: The multivariate analyses did not include important clinicopathologic prognostic factors, such as sex, anatomic site, and mitotic index, among others. A complete case analysis can be biased if individuals with missing data are not typical of the whole sample; use of missing data imputation methods could have overcome this limitation.

Incomplete risk of bias assessment: The risk of bias assessment omitted an entire patient cohort, despite it contributing approximately 25% of the estimated effect size weight. Because few methodologic details are provided, the quality of a significant proportion of cases cannot be assessed by readers.

Publication bias: We analyzed data in Figure 1, *A* using the Egger regression test and by inspecting a funnel plot. We identified funnel plot asymmetry and evidence suggesting small-study effects (intercept, 1.279; $P = .042$).

Meta–conflicts of interest: The majority of the study authors reported a financial conflict of interest for this work and were the authors of many (or all) of the included studies. This has been shown to increase the likelihood that included studies are rated as having a low risk of bias.[7] Spin—that is, differences between the results and conclusions—has also been shown to be related in trend toward the inclusion of one's primary studies in a systematic review.[8]

The evidence supporting the clinical validity of a prognostic factor should not be interpreted as evidence of clinical utility. The demonstration of a statistically significant hazard ratio in appropriately designed studies using multivariate analysis is an important initial step in the pathway toward demonstrating potential clinical utility. Ultimately, however, it must be shown to add incremental clinical value to pre-established and readily available prognostic factors in a cost-effective manner. This is best accomplished via a prognostic model that gives a personalized absolute risk prediction of an outcome. To facilitate these efforts, it would be helpful if the melanoma community identified consensus-driven, prespecified outcome risk thresholds that justify a change in treatment. Although a randomized controlled trial demonstrating an improvement in patient outcomes with the use of such a prognostic factor/model is ideal, other methods, such as net benefit and decision curve analysis, can suggest clinical usefulness if treatment risk thresholds are appropriately defined.[9]

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Funding source: Supported in part by a grant from the National Cancer Institute/National Institutes of Health (P30-CA008748).

Conflicts of interest: None disclosed.

IRB approval status: Not applicable.

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https://doi.org/10.1016/j.jaad.2020.04.186