The authors state that the Pathwork TOO test showed 97% accuracy in determining the site of origin of a tumor, in contrast with immunohistochemical staining, which has a reported accuracy of 75% to 88%,2,3 suggesting that the TOO Test is a better discriminator of the site of origin of tumors. However, in our opinion, this is not a fair comparison. The case types studied are entirely different in these studies. Immunohistochemical panels reached more than 95% accuracy in the correct identification of sites of origin of lung, colon, breast, and prostate carcinoma for which relatively specific and sensitive markers are available. In fact, it would be reasonable to assume that these numbers have only been bettered by the introduction of newer markers, eg, napsin A (lung) and PAX8 (female genital tract). The failure of immunohistochemical staining is limited to relatively specific situations, eg, inability to conclusively identify the site of origin of related tumors such as gastric, pancreatic, and biliary carcinoma for which specific immunohistochemical markers are not available. These “difficult to nail” tumor types were not included in this study, and, as such, the percentages cited are not comparative. In fact, application of an appropriate immunohistochemical panel would have been discriminatory in all 6 cases in which the TOO Test’s performance was cited as being superior. Indeed, the authors concede as much by using immunohistochemical results as confirmatory of the TOO Test result in some cases.

The authors state that the TOO Test could save cost by avoiding unnecessary immunohistochemical staining and expensive radiologic testing. These statements, too, are questionable. Immunohistochemical staining, even in the form of a 7- to 10-panel test, is much cheaper than the $3,500 cost of the TOO Test. In addition, the ease of testing, quick results, and ability to do the test in house without specialized machinery or expertise, make immunohistochemical staining the initial test of choice in the analysis of tumors of unidentified primary site. In fact, we believe that it is standard clinical practice to confirm the undifferentiated nature of a malignancy with a basic immunohistochemical panel, as several stains (eg, melanoma markers, thyroid transcription factor-1, CDX2, napsin, and PAX8) have excellent discriminatory value. Indeed, recent guidelines in certain circumstances more or less require confirmation of the site of origin with at least a basic immunohistochemical panel.5 It is therefore disturbing that cases were labeled as “undifferentiated” or of “unclear primary origin” without using available antibodies and makes one wonder if the cases were retrieved from an era that predates modern immunohistochemical analysis. (The authors do not state the period for which the cases were collected.)

Likewise, the authors’ statement about expensive imaging having been done to determine site of origin is puzzling, especially because in several cases the need for additional radiologic testing would have been obviated if an adequate panel of cheap immunohistochemical tests had been used at the outset. The authors provide no proof to support their statement that these studies were done solely to determine the site of origin of tumor. These costs truly may not be avoidable in that radiologic studies help determine the extent of disease and appropriate treatment options (eg, a solitary metastases may be amenable to resection). The cost-benefit analysis provided is therefore flawed.

In the end, the study design here is artificial and does not replicate actual responsible 21st century clinical practice. Rather, this study reflects a mock setting wherein frozen tissue is dissected on biopsy material (although we are aware that the TOO Test is marketed for paraffin-embedded material), and history, radiologic findings, and prior material are not considered in the algorithm. The TOO Test may well add to our armamentarium of tests that help identify the site of origin of tumors, but this study fails to answer the question that vexes us too often. The question is not whether the new test is better than no additional test, but rather whether the new test is better than the time-tested alternative currently being used. Subset analysis to define a truly cost-effective approach remains to be done.

This study also raises a broader question to the Journal of about how information should be evaluated and displayed when a commercial provider has sponsored a study and stands to benefit from the results of the study. It is surprising that the Journal did not require a more detailed disclosure to the readers of the nature of the sponsorship provided by the company in question, but instead allowed the display of the information inconspicuously at the end of the article, in the same paragraph as the reference to support by the National Institutes of Health. Indubitably, this article runs the risk of prominent display in the marketing materials for the test, with or without the explicit consent of the Journal or the authors. It will likely be marketed to clinicians who cannot take the time to evaluate critically the 2 tests that are compared and will be impressed by the “non–white paper” nature of the results, that the results were published in a prominent

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In their letter, Parkash et al suggest that the conclusions from our recent clinical verification report of the Pathwork TOO Test\(^1\) may be overreaching. Specifically, Parkash et al consider that our findings of the molecular test’s performance, of 97% (95% confidence interval [CI], 80.4%-99.8%) agreement with the complete diagnosis, which included additional immunohistochemical studies and computed tomography (CT) results. In our data set, the TOO Test showed 79% agreement (95% CI, 59.7%-91.3%) with the initial histopathologic diagnosis, which used a limited number of immunohistochemical stains for most cases.

We regret any confusion that was caused by our omission of the specific initial immunohistochemical studies used in each of our cases. The choice for initial immunohistochemical workup in each case was based on clinical and imaging information available at the time the tissue sample was obtained. As noted in our Table 3, in most cases this initial workup yielded an accurate diagnosis of the lesion; TOO was performed on fresh frozen tissue.

References


The Authors’ Reply

In their letter, Parkash et al suggest that the conclusions from our recent clinical verification report of the Pathwork TOO Test\(^1\) may be overreaching. Specifically, Parkash et al consider that our findings of the molecular test’s performance, of 97% (95% confidence interval [CI], 80.4%-99.8%) agreement with the complete diagnosis, are contrasting the accuracy of previously published, well-established immunohistochemical algorithms (75%-88%).\(^2,3\) Notably, our findings are in agreement with recently published performance assessments of this molecular test, such as an overall accuracy of 90% (95% CI, 73%-97%)\(^4\) and a 94.1% agreement with available diagnoses in cytologic specimens.\(^5\)

Parkash et al suggest that our results do not seem to arise from a fair comparison. Actually, our study did not intend to compare the performance of the TOO Test with that of immunohistochemical panels alone. As directed by the Clinical Laboratory Improvement Amendments of 1988 and as recommended by the Clinical and Laboratory Standards Institute,\(^6\) the analytic and clinical performance of US Food and Drug Administration (FDA)-cleared assays must be verified before implementation of the test. Thus, our intent was to perform a clinical verification of the FDA-approved TOO Test by assessing this molecular test’s performance on poorly differentiated or undifferentiated tumors based on the initial histopathologic diagnosis and with the complete diagnosis, which included additional immunohistochemical studies and computed tomography (CT) results. In our data set, the TOO Test showed 79% agreement (95% CI, 59.7%-91.3%) with the initial histopathologic diagnosis, which used a limited number of immunohistochemical stains for most cases.

We regret any confusion that was caused by our omission of the specific initial immunohistochemical studies used in each of our cases. The choice for initial immunohistochemical workup in each case was based on clinical and imaging information available at the time the tissue sample was obtained. As noted in our Table 3, in most cases this initial workup yielded an accurate diagnosis of the lesion; TOO was performed on fresh frozen tissue.

Correspondence

peer-reviewed journal, and that the study was conducted at an institution of significant repute. With this publication, it seems that time has arrived for pathology journals to develop policies to require an evaluation/comment regarding the potential for unconscious bias in studies with commercial sponsors. Bias is a risk in any study, but studies with industry sponsors are particularly prone to bias and need to be evaluated even more carefully and critically than unsponsored studies. Anatomic pathology has been sheltered from industrial sponsorship for much of its existence as a field, but with the advent of molecular medicine we are likely now (especially at large academic institutions) to be courted aggressively by industry, as we are “keepers of the tissue.” There must be specific disclosure of the nature of the sponsorship and a requirement to display this information in the abstract (since reading the entire article is a luxury that many a busy pathologist or physician cannot afford).

In the spirit of full disclosure, we would like to declare that we have used the Pathwork TOO Test in a handful of cases. We used the test in cases in which the tissue of origin of a malignancy could not be established after exhaustive clinical and immunohistochemical testing, and the TOO Test did not add as much as we would have liked. In 1 case, testing of 2 different samples from the same patient came up with different results (melanoma and no specific first choice), which were not consistent with the clinical/histologic evaluation of the case, and resulted in additional testing for the patient, with much consternation on the part of clinician and pathologist. This case was eventually diagnosed as epithelioid sarcoma after consultation and performance of INI1 staining. Having said that, we continue to try to keep an open mind and consider the test in cases in which standard clinicopathologic evaluation is unable to provide the correct answer.

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