

Multicenter Validation of a 1,550-Gene Expression Profile for Identification of Tumor Tissue of Origin

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PURPOSE

Malignancies found in unexpected locations or with poorly differentiated morphologies can pose a significant challenge for tissue of origin determination. Current histologic and imaging techniques fail to yield definitive identification of the tissue of origin in a significant number of cases. The aim of this study was to validate a predefined 1,550-gene expression profile for this purpose.

METHODS

Four institutions processed 547 frozen specimens representing 15 tissues of origin using oligonucleotide microarrays. Half of the specimens were metastatic tumors, with the remainder being poorly differentiated and undifferentiated primary cancers chosen to resemble those that present as a clinical challenge.

RESULTS

In this blinded multicenter validation study the 1,500-gene expression profile was highly informative in tissue determination. The study found overall sensitivity (positive percent agreement with reference diagnosis) of 87.8% (95% CI, 84.7% to 90.4%) and overall specificity (negative percent agreement with reference diagnosis) of 99.4% (95% CI, 98.3% to 99.9%). Performance within the subgroup of metastatic tumors ($n = 258$) was found to be slightly lower than that of the poorly differentiated and undifferentiated primary tumor subgroup, 84.5% and 90.7%, respectively ($P = .04$). Differences between individual laboratories were not statistically significant.

CONCLUSION

This study represents the first adequately sized, multicenter validation of a gene-expression profile for tissue origin determination restricted to poorly differentiated and undifferentiated primary cancers and metastatic tumors. These results indicate that this profile should be a valuable addition or alternative to currently available diagnostic methods for the evaluation of uncertain primary cancers.

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