

# Validation of a microarray-based gene expression test for tumors with uncertain origins using formalin-fixed paraffin-embedded (FFPE) specimens.

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Abstract:

**Background:** Microarray-based gene expression has been validated as an aid in the diagnosis of tumors with uncertain origins when the specimen is frozen tissue. Microarray use has been largely limited to RNA derived from frozen specimens. This study evaluated performance of a microarray-based test in identifying the tumor type in FFPE specimens. **Methods:** ZFFPE human tumor specimens (n=405) representing the 15 tissue of origin sites on the Pathwork<sup>®</sup> Tissue of Origin Test panel were blinded and evenly distributed between two independent processing labs. All specimens consisted of a 10- $\mu$ m-paraffin curl containing at least 60% viable tumor and were either metastatic or poorly differentiated primaries. Each specimen was processed through RNA extraction, amplification, labeling, hybridization to a Pathchip<sup>®</sup> microarray, and was scanned to generate a qualified data file. A pre-specified classification algorithm utilizing more than 1500 genes was applied to each data file to yield Similarity Scores corresponding to the 15 tissues on the test panel. Results were then unblinded and compared to the available diagnoses. **Results:** Of the 405 specimens, 352 yielded qualified data files (87%). Based on the top Similarity Score, the overall agreement with available diagnoses was 89% (95% CI, 85%-92%) and for each specimen an average of 12 out of 15 tissues could be ruled out with > 99% probability. Results for all tissue types were highly informative with diagnostic odds ratios ranging from 178 to 28509. Performance was similar for metastatic (n=150; 91% agreement) and poorly differentiated primary specimens (n=202; 87% agreement). **Conclusions:** The large size of this study allows an accurate estimate of the confidence of test predictions for both ruling in and ruling out tissues as likely sites of primary origin. The Pathwork Tissue of Origin Test makes the potential benefits of microarray-based gene expression tests for tumors with uncertain origins available for use with the most common type of histology specimen, FFPE.