Blinded comparator study of immunohistochemistry (IHC) versus a 92-gene cancer classifier in the diagnosis of primary site in metastatic tumors.

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Abstract:

**Background:** Metastatic tumors of uncertain or unknown origin pose diagnostic and therapeutic challenges. Accurate tumor classification is fundamental to inform predictive biomarker testing and optimize therapy. Standard of care employs IHC analysis for tumor classification that is varied in approach and interpretation. More recently, gene expression-based tests have been proposed as diagnostic aids. This study directly compared the diagnostic accuracy of IHC vs molecular classification with a 92-gene RT-PCR assay (CancerTYPE ID) for determination of primary tumor site.

**Methods:** In this prospectively-defined, blinded study, 132 high grade, metastatic cases were selected by City of Hope (COH). Cases were reviewed and reference diagnoses established by clinical correlation (eg, patient history, imaging). Blinded FFPE sections were evaluated by either IHC or the 92-gene RT-PCR assay. Results were scored within a clinically-relevant categorization system designated by COH for main tumor type and subtype. The primary endpoint was concordance with the reference diagnosis. Study unblinding and data analysis were conducted by an independent third party.

**Results:** Final analysis included 123 cases (mean age±SD: 61.2±14.4y, 52% female; grades 3/4; 90% metastatic); 9 cases were excluded (8: RNA quality; 1: insufficient tumor tissue). The 92-gene assay demonstrated an overall accuracy of 78% for tumor classification vs 68% for IHC (P = 0.017). For tumor subclassification, the 92-gene assay correctly identified 72% of tumors compared to 61% with IHC (P=0.029). Sensitivities were similar for GI (77%) and kidney (77%). The 92-gene assay demonstrated higher sensitivities for lung (75% vs 67%), urinary bladder (75% vs 42%), and breast (73% vs 55%). Mean IHC use was 7.8 stains per case (median: 8, range: 2-15).

**Conclusions:** This is the first study to directly compare the diagnostic accuracy of IHC vs molecular classification. Results from this blinded series of high grade metastatic cases demonstrate superior accuracy with the 92-gene assay vs standard of care IHC, and strongly support the diagnostic utility of molecular classification in difficult to diagnose metastatic cancer.
multisite validation of a 92-gene molecular classifier: diagnostic accuracy and clinical utility in metastatic cancer.

background: accurate tumor classification is increasingly critical to individualized care as patient outcomes improve with use of targeted cancer therapies and predictive biomarkers. in metastatic cancers of uncertain or unknown origin, identification of a primary site remains equivocal in a significant number of cases. gene expression signatures may improve accuracy and specificity of tumor classification, however, large-scale, blinded validation studies that demonstrate stable performance in metastatic and poorly differentiated cases are currently lacking. methods: seven hundred and ninety cases (51% female, 44% metastatic, 63% grade 2 and 3, 14% limited tissue specimens) representing 28 tumor types and 50 subtypes were processed and adjudicated between mayo clinic, ucla and massachusetts general hospital. blinded ffpe tumor sections were submitted and tested using a 92-gene rt-PCR assay (CancerTYPE ID, bioTheranostics Inc.). molecular predictions were evaluated for concordance with the reference diagnosis; diagnostic accuracy between clinical subsets was compared.

results: the 92-gene assay demonstrated overall sensitivities of 87% for tumor classification and 82% for subtyping. forty-seven (5.9%) cases were considered unclassifiable. comparative analysis of performance between metastatic (n=329) and primary (n=414) tumors showed no statistically significant difference in accuracy (85% vs 88%, p=0.16). Similarly, no significant decreases in performance were observed across histological grades (p=0.58) and when comparing limited tissue to excisional biopsy specimens (p=0.16). strong precision was demonstrated for accurate identification of a primary tumor in tissues biopsied from common metastatic sites, reported as positive predictive values of 100% for lung, brain and peritoneum, 92% for ovary and 80% for liver. conclusions: results from this multisite, blinded study validate the diagnostic accuracy of the 92-gene assay for classifying a diverse set of tumors, and support its clinical utility in the diagnosis of metastatic tumors to determine tissue of origin, and in the differential diagnosis of metastatic vs new primary disease.
Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients (pts) with carcinoma of unknown primary site (CUP): Results of a prospective Sarah Cannon Research Institute (SCRI) trial.

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Abstract:

Background: Tumor profiling is an emergent technique to determine tissue of origin in CUP patients. However, the value of these predictions in improving treatment efficacy is unknown. In this prospective trial, we used tumor profiling results to direct site-specific therapy for CUP pts.

Methods: A 92-gene RT-PCR assay (CancerTYPE ID; bioTheranostics, Inc.) was performed on tumor biopsies from previously untreated CUP pts who consented. When a tissue of origin was predicted, pts who were treatment candidates were assigned standard site-specific first-line therapy.

Results: Between 10/08 and 12/11, 289 pts were enrolled, 252 had successful assays performed, and 247 (98%) had a tissue of origin predicted. 224 pts were eligible for treatment; 197 pts received assay-directed treatment. 120 of 224 treated pts (54%) had assay diagnoses of tumor types known to derive substantial benefit from standard site-specific treatment (bladder 27, colorectal 26, NSCLC 24, breast 10, ovary 10, kidney 9, prostate 4, germ cell 4, others 6 (3 sites), while 104 pts (46%) had assay diagnoses of relatively resistant tumors (biliary tract 45, pancreas 12, gastroesophageal 10, liver 7, sarcoma 5, cervix 5, others 20 (8 sites). Median OS for all treated pts was 10.8 months (mos); OS for 197 pts with assay-directed treatment was 12.2 mos (versus 6.0 mos for 27 pts receiving empiric therapy). Median OS was better in the 120 pts with assay diagnoses of more responsive tumor types (12.8 vs 7.4 mos; p = .027).

Median OS (mos) in specific subgroups: pancreas 9, kidney 12, colon 12, NSCLC 16, ovary 30.

Conclusions: This is the first prospective trial in which molecular profiling has directed site-specific therapy in CUP pts. Assay-directed therapy in 197 pts produced a median OS (12.2 mos) that compares favorably with previous empiric CUP therapy. CUP pts predicted to have more responsive tumor types had longer survival compared to less responsive types, suggesting accurate identification by the assay. These results strengthen the rationale for molecular profiling in CUP management.