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Use of a 92-gene Molecular Classifier to Predict the Site of Origin for Primary and Metastatic Tumors with Neuroendocrine Differentiation

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Background: A diagnosis of neuroendocrine carcinoma (NEC) is typically straight-forward using a combination of morphology and immunohistochemical stains (eg. synaptophysin, chromogranin), however, the tumor site of origin may remain elusive in a metastatic presentation. Neuroendocrine tumor subtyping has important implications for staging and management. This study describes the use of a 92-gene molecular cancer classifier for neuroendocrine tumor subtyping.

Methods: Seventy-five (44 metastatic and 31 primary) formalin-fixed, paraffin-embedded tumor samples were selected after a 3-pathologist adjudicated review. Clinicopathologic diagnoses were classified as follows for comparison to the molecular classifier output: Intestinal NEC (n=12), high-grade pulmonary NEC (small cell or large cell, n=11), low-grade pulmonary NEC (pulmonary carcinoid, n=11), Merkel cell carcinoma (n=10), pancreatic NEC (n=10), pheochromocytoma/paraganglioma (n=10), and medullary thyroid carcinoma (n=11). Samples were tested in a blinded fashion using the CancerType ID® 92-gene classifier (bioTheranostics, Inc), which makes tumor type predictions based upon expression measurement of 87 gene targets and 5 reference genes by quantitative PCR. The top classifier prediction was compared to the reference diagnosis.

Results: The classifier correctly predicted the reference subtype diagnosis in 71 of 75 cases (95%). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for predicting individual subtypes are shown in Table 1. Three of the 4 incorrectly predicted cases were correctly predicted to the neuroendocrine carcinoma level, but were assigned an incorrect subtype.

Conclusion: The 92-gene classifier demonstrated excellent accuracy for subtyping tumors with neuroendocrine differentiation. While this study did not adjust for subtype prevalence in practice, these results show promise for use in classifying neuroendocrine tumors of unknown primary site.

Table 1. 92-gene Classifier Subtype Performance

Subtype	N	Match	Sens	Spec	PPV	NPV
Intestinal	12	12	1.00	1.00	1.00	1.00
Lung high grade	11	10	0.91	1.00	1.00	0.98
Lung low grade	11	10	0.91	1.00	1.00	0.98
Merkel cell	10	10	1.00	0.97	0.83	1.00
Pancreas	10	8	0.80	0.98	0.91	0.97
Pheo/paraganglioma	10	10	1.00	1.00	1.00	1.00
Thyroid medullary	11	11	1.00	1.00	1.00	1.00
Total	75	71	0.95			