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Blood Neuroendocrine Transcript Analysis for the Diagnosis and Clinical Status Assessment of Bronchopulmonary Neuroendocrine Tumors

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BACKGROUND: We evaluated the clinical utility of a 51 NET-specific transcript set (NETest) in blood to diagnose bronchopulmonary (BP) neuroendocrine tumors (NET) and define their clinical status.

METHODS: Gene expression was evaluated in publicly-available BPNET transcriptomes (GSE35679), BPNET tumor tissue and cell lines. Whole blood from 160 carcinoids, 109 lung disease samples (COPD: n=18; adenocarcinoma: n=54; squamous cell carcinoma: n=37) and 90 control samples were evaluated. Whole blood transcript levels (real-time PCR) and plasma chromogranin (ELISA-Euro Diagnostica) were examined. Scored gene expression (0-100%) and CgA levels (upper limit of normal: 108ng/ml) were evaluated and compared by non-parametric, ROC, Fisher's test and decision curve analysis. RECIST was used to evaluate clinical status.

RESULTS: All 51 marker genes were identified in BPNET transcriptomes, tumor tissue and cell lines and significant correlation was noted between matched tumor and blood values (R2: 0.38–0.64, p<0.001). Circulating gene scores were

highest in carcinoids (48.5±2.2%) versus other neoplasia (mean: 19.6-23.7%, $p<0.0001$), COPD (23±0.8, $p<0.0001$) and controls (5.6±0.6, $p<0.0001$). The AUC for differentiating carcinoid from controls was 0.98±0.01. Scores were examined in the context of clinical status and highest (72±3.2%) ($p<0.0001$) in progressive disease (n=55), versus stable disease (n=105; 34±2%) and surgical cures (n=6, 10±1%). The AUC for differentiating clinical status was 0.89±0.03. CgA, although elevated (only 40%) in carcinoids (728±195ng/ml versus 64±22ng/ml in controls) was not related to clinical status (AUC: 0.51±0.05). Decision Curve Analysis confirmed the utility of the multianalyte gene marker panel as a diagnostic (>90% effective versus <20% for CgA).

CONCLUSION: A circulating signature of NET-specific marker genes can be used to accurately diagnose bronchopulmonary “carcinoids” and has clinical utility in identifying progression. In contrast, CgA is inadequate as a diagnostic marker and fails to define the clinical status.