

# Blood Gene Transcript Analysis Diagnoses Bronchopulmonary NETs and Identifies Progressive Disease

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**Background:** Bronchopulmonary (BP) NETs comprise ~30% of all NETs and are classified into 4 groups: typical (TC); atypical carcinoid (AC); large cell NEC and small cell cancer. Differentiating between atypical (AC) and typical (TC) can be challenging. Ki67 (high grade NECs) and somatostatin receptor (SSTR) expression is of some value in guiding therapy. Biomarkers remain of equivocal value and limited clinical utility.

**Methods:** BP-NETs (n=94; complete resection; disease free: n=6, stable disease (SD): n=39; progressive disease (PD): n=49); other lung disease (non-neoplastic: n=33; neoplastic: n=3); normal controls n=84). PD was established by clinical and RECIST criteria. NETest measurement utilized qPCR: risk scale 0-100%; low (<40%) and high activity risk cutoffs (>80%). Multianalyte algorithmic analysis included 51 genes with inclusion of SSTRs (SSR1,3,5) "omic" was undertaken. CgA measured by ELISA (normal <109ng/ml). Analysis by X2 tests and ROC (area under curve [AUC]).

**Results:** In all BP-NETs irrespective of TC or AC, NETest was positive (88/88, 100%). Other neoplastic and non-neoplastic lung disease (3/36, 8% positive) (AUC: 0.88±0.03, p<0.001) as were controls (30/33, 90%) (AUC: 0.97±0.01, p<0.0001). A NETest value of >40% defined progressive disease (PD) vs stable disease (SD) in 80% (p<0.0001, AUC: 0.87±0.04). Surgical cures and controls were all negative (NETest<14%). Combination of NETest and SSTR "omic" gene defined clinico-histological groups in 94%: PD/AC (92%; 35/38), PD/TC (100% 11/11), SD/AC (67%, 6/9), SD/TC (100%, 30/30). Only 50% of BP-NETs were CgA positive (X<sup>2</sup>=20.1, p<0.001). CgA increase did not predict progression.

**Conclusion:** A blood-based NETest positively identified BPNETs (100%) and negatively controls and lung disease (<10%). Progressive disease, stable disease and no disease (curative surgical resection) can be accurately identified (94%). BP-NET clinico-histological groups can be accurately identified by NETest+SSTRomic analysis in 94%. Blood-based genomic information will facilitate precise lung NET characterization and provide molecular information of clinical utility.