A blood-based measurement of neuroendocrine tumor transcripts (NETest) accurately identified BPNETs with disease (100%) and differentiated neoplastic and non-neoplastic lung disease. The NETest accurately identified clinico-histological groups and can be used to facilitate TC/AC clinical characterization.

Background
Broncho-Pulmonary (BP) NETs comprise ~30% of all NETs and are classified into four groups: typical carcinoid (TC), atypical carcinoid (AC), large cell NEC (LCNEC) and small cell lung cancer (SCLC). Differentiating TC and AC can be challenging as these tumors comprise a spectrum of indolent to aggressive behavior. Imaging, histology (Ki67 and high grade NECs) and biochemistry e.g., circulating chromogranin A levels, are limited in defining malignancy or progression.

Aim
To assess the NETest in BP-NETs and evaluate its role in delineating progressive disease.

Methods
Neuroendocrine lung neoplasia (n=125; BPNETs (n=114), LCNEC (n=6), SCLC (n=5)); lung neoplasia (adenocarcinoma (n=7), squamous cell carcinoma (n=5); non-neoplastic lung disease (COPD: n=18) and healthy controls (n=90). Measurements were blood NET by qPCR: CgA by ELISA (EuroDiagnostica, normal <109ng/ml); disease status was by imaging. BPNETs were typical TC: n=64, atypical AC: n=44 and complete remission (CR: n=6). Seventy-four with disease were classified as stable (SD); progressive disease (PD n=34). 56% AC were PD, 23% TC were PD. Clinico-histological groups were AC/SD or AC/PD; TC/SD or TC/PD by RECIST. Analysis was by 2-tailed Mann-Whitney U-test, Chi² tests and ROC-statistics.

Results
NETest was positive in all BPNETs (100%) irrespective of TC or AC. CRs were all low (<14%), within the normal range. Non-neoplastic lung disease exhibited the highest values of controls (24±2.5%). All NE-neoplasia exhibited significantly elevated NETest (p<0.005). The AUC for differentiating BPNETs from lung disease controls was 0.90±0.03, p<0.0001. NETest predicted clinical status (SD: 38±3% or PD: 74±4%, p<0.0001) irrespective of histological type (AUC: 0.86±0.04, p<0.0001). CgA was non-informative. While it was significantly elevated in COPD (151±37ng/ml) and BPNETs (804±240ng/ml) (both p<0.002 versus healthy controls), the AUC for differentiating BPNETs from lung disease controls was only 0.58±0.05, p=NS. In addition, CgA levels were not able to differentiate PD (397±207ng/ml from SD (mean: 1016±371ng/ml; p=0.71) (AUC: 0.51±0.06, p=NS).

Conclusion
- A blood-based NETest accurately identified neuroendocrine neoplasia lung diseases.
- BPNETs were identified (100%) by the NETest.
- NETest accurately identified BPNETs with PD irrespective of histological status.
- CgA was non-informative.