Circulating neuroendocrine gene transcripts – the NETest – accurately identify GEP-NETs, are decreased by surgery and predict tumor progression and recurrence

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Principal Message

A blood-based NET transcript analysis (NETest) has clinical utility in diagnosis and identification of either residual disease or disease progression. Blood-based measures of tumor activity provides pathobiological information that amplifies image-based assessment of GEP-NET disease.

Background

A blood-based multigene (51) transcript algorithmic analytic test (MAAA) correlates with tumor tissue levels and provides a neuroendocrine tumor (NET) gene signature. Morphologic and functional imaging is the standard of care for NET localization and for assessing therapeutic efficacy.

Aim

Evaluated the concordance between the NETest and imaging and whether blood transcripts are a prognostic marker.

Methods

GEP-NETs (*n*=180) of the small intestine: *n*=93, pancreas: *n*=52, large intestine: *n*=11, stomach: *n*=3, appendix: *n*=2 and CUP: *n*=19 were studied. Grading was: G1: *n*=80, G2: *n*=86, no data: *n*=14. Somatostatin receptor imaging (SRI) was available in 103 (57%). Seventy-seven (43%) had CT/MRI and grading assessment (RECIST 1.0: median 251 days follow-up: range 31-422). NETest (qPCR and MAAA) defines disease activity risk: negative <14%, low <40%. CgA (ELISA): normal <109ng/l). Statistical analyses: Chi^2, performance metrics analysis and progression-free survival (Kaplan-Meier).

Results

NETest was elevated in 175 (97%) vs CgA in 94 (52%) [X^2=94.1, p<0.0001]. NETest was 100% concordant with CT/MRI and 95% with SRI. Twelve patients with CT/MRI-proven absence of disease (5-years post-surgery) exhibited NETest<14% and normal CgA. Metrics for NETest and imaging (*n*=180): sensitivity: 97%, specificity: 100%, PPV: 100% and NPV: 71%. CgA metrics: 52%, 100%, 100% and 12%. Surgery significantly (p<0.05) decreased NETest levels and correlated with tumor volume (R^2=0.29, p=0.02). Post-surgery NETest elevation (>40%) predicted disease recurrence in 100% (≤6 months). NETest was concordant with baseline disease status (RECIST) in 87%; CgA=54% (X^2=12.3, p<0.001). A low NETest (<40%) accurately predicted progression free survival and was significantly different (p=0.01, X^2=6.57) compared to a NETest>40% (undefined v 253 days; HR=3.36. CgA was non-predictive (p=0.22).

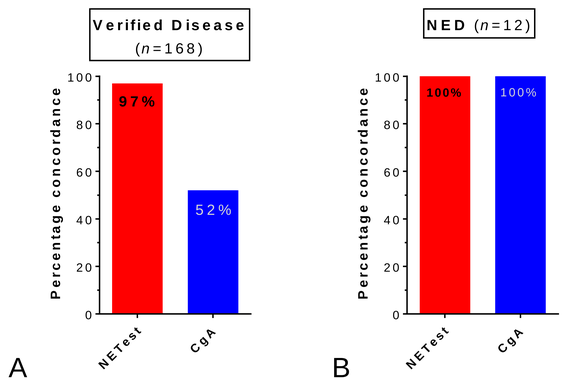

Figure 1: Concordance between imaging and NETest or chromogranin A (CgA).
1A. NETest was positive (≥14%) in 97% of subjects with histologically verified disease. CgA was elevated (>108ng/ml) in 52%. χ^2=94.1, p<0.0001.
1B. NETest levels were normal in 100% of subjects with no evidence of disease (NED), five years after surgery. CgA levels were normal in all 12.

A positive NETest is concordant with GEP-NET disease

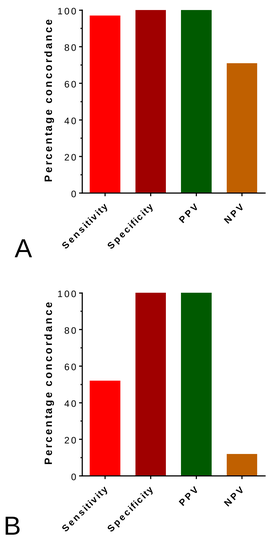

Figure 2: Metrics for NETest and CgA and GEP-NET disease (*n*=180).

2A. A positive NETest (≥14%) had sensitivity, specificity and positive predictive value (PPV) >90% for GEP-NET disease. The negative predictive value (NPV) was 70%.

2B. For CgA, the specificity and PPV was 100% for an elevated measure (>108ng/ml). The sensitivity and NPV were <50%.

NETest metrics outperform CgA for identification of GEP-NET disease

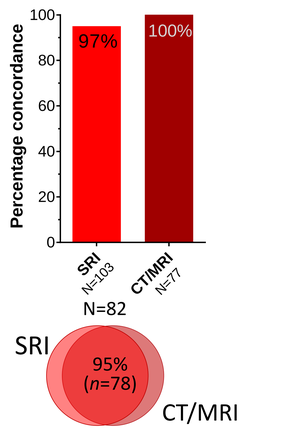

Figure 3: Concordance between Imaging and NETest
Positive NETest was concordant with somatostatin receptor imaging (SRI) in 97% of cases and CT/MRI (100%). When both modalities were available for the same subject (*n*=82), the concordance was 95%.

NETest positivity (≥14%) correlates with Image-detected disease

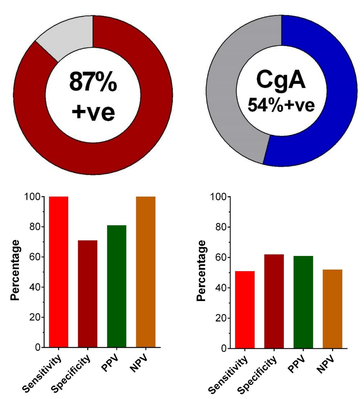

Figure 4: Disease status and biomarkers (baseline)
A positive NETest correlated with clinical status (RECIST – stable or progressive disease) in 87% of cases. Elevated CgA correlated in 54% of cases. χ^2=12.3, p<0.001 (*top*). Metrics for NETest and RECIST were >80% for sensitivity, PPV and NPV. Metrics for CgA were all <60% (*bottom*).

NETest provides a sensitive measure of disease status at baseline

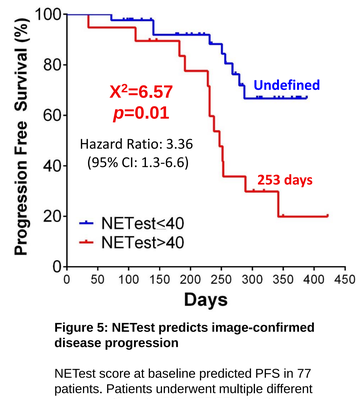

Figure 5: NETest predicts image-confirmed disease progression

NETest score at baseline predicted PFS in 77 patients. Patients underwent multiple different treatment [SSA (*n*=53); STZ/5FU (*n*=4); Everolimus (*n*=2); untreated (*n*=18)].

NETest >40% associated with a median PFS of 253 days (8.3 months).
Median PFS was not achieved when baseline NETest ≤40%.

Elevated NETest (>40%) predicts and is prognostic for tumor progression

Conclusion

- A blood-based NET transcript test has threefold clinical utility: diagnosis (97%), identification of residual disease (100%) and disease progression (100%).
- It accurately correlated with image-proven NET disease and surgical resection.
- NETest has clinical utility in the monitoring of NET disease.

NANETs Jackson Hole, September 30, 2016