Neuroendocrine Tumor Blood Transcript Analysis, the NETest, Predicts Gastroenteropancreatic Neuroendocrine Tumor Disease Status and is Prognostic for Progressive Disease

M. Pavel[#], H. Jann[#], V. Prasad[#], I Drozdov*, M. Kidd*, I. Modlin*

[#]Charité - Campus Virchow-Klinikum, Universitätsmedizin Berlin, Germany
*Wren Laboratories, Branford CT, USA

Principal Message

NETest correlates with clinical disease status and levels (≥70%) are prognostic for well-differentiated GEP-NET progression (per RECIST).
NETest <40% correlated with disease stability over ~5-years identifying this molecular signature also is predictive.
Patients clinically categorized as stable with high NETest levels (>70%) develop disease progression in 100% of cases within 2 years.

Background

A key issue in GEP-NETs is early identification and prediction of disease progression. Clinical evaluation and imaging are limited due to the lack of sensitivity and disease indolence. We assessed the utility of the NETest as a predictive and prognostic marker of progression in a long-term follow-up study.

Methods

GEP-NETs (*n*=31 followed for a median 4 yrs (2.2-5.4). WHO tumor grade/stage Grade I: *n*=15, Grade II: *n*=16; 31 (91%): stage IV. Baseline and longitudinal imaging and biomarkers were available and progression defined (RECIST 1.0). NETest: qPCR and multianalyte algorithmic analysis (disease activity scaled 0-100% with low <40% and high activity risk cutoffs >80%); CgA: RIA (normal <150µg/l); PFS: Kaplan-Meier analysis. A quantitative disease activity score was also developed (cumulative sum of disease activities (*s*) across all preceding time points) and affinity propagation algorithms used to cluster longitudinal patient disease activity profiles.

Results

At baseline, 100% were NETest-positive and CgA was elevated in 50%. Baseline NETest (>80%) was significantly associated (p=0.01) with disease progression (median PFS 0.68 yrs vs. 2.78 yrs with <40% levels). NETest was more informative (96%) than CgA changes (Δ>+25%) in consistently predicting disease alterations (40%, $p<2x10^{-5}$, $Chi^2=18$). The NETest had an earlier time-point change than imaging (1.02±0.15 years). Baseline NETest levels >40% in stable disease were 100% prognostic of disease progression vs CgA ($Chi^2=5.0$, $p<0.03$). Baseline NETest values <40% accurately (100%) predicted stability over 5-yrs (p=0.05, $Chi^2=3.8$ vs. CgA).

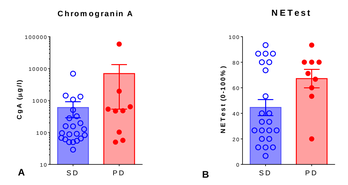

Figure 1
Baseline blood-based biomarker expression (*n*=31).
1A) Groups were progressive disease (PD) at baseline (*n*=9) or stable disease (SD: *n*=22). CgA levels trended (p=0.07) to be higher in the PD group at baseline. Mean±SEM.
1B) NETest levels were significantly elevated in the PD group at baseline (p=0.05). Mean±SEM.

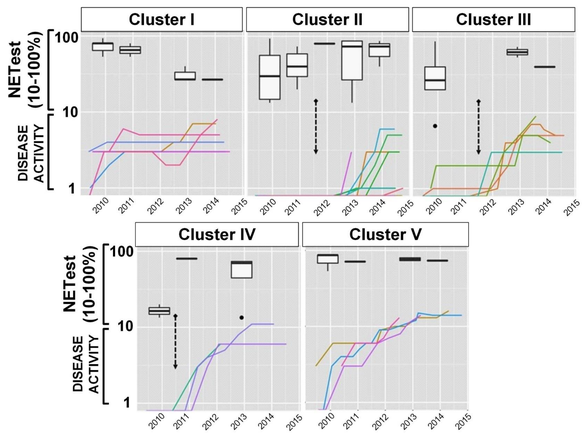

Figure 2
Individual Longitudinal disease activity profile clusters (I-V) defined by the Affinity Propagation Cluster (APC) algorithm.
Each of the 5 clusters (I-V) represents a distinct patter of disease activity over time. Each colored line reflects the disease activity value of an individual over the five-year time course. The boxplots (upper component of each graphic) depict the NETest measurements over time. NETest values ≥50% were associated with disease progression. The dashed vertical arrows represent the time point correlation between alterations in the NETest scores and assigned disease activity values as determined by the APC algorithm.
Cluster I identifies patients who exhibited consistently stable disease.
Clusters II, III, IV identify patients who were stable at entry but developed disease progression at different time points: Cluster II at 4 years; Cluster III at 3 years and Cluster IV at 2 years.
Cluster V represents patients with progressive disease from year 1.

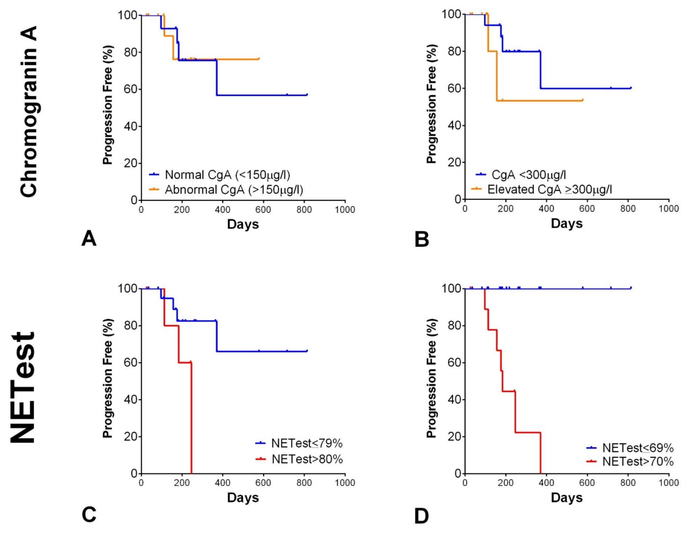

Figure 3
Blood-based biomarkers and relationship to survival assessed using Kaplan-Meier analysis.
3A) PFS was not associated with elevated (>150ug/l) CgA levels.
3B) PFS was not linked to abnormally elevated CgA (≥300ug/l).
3C-D) PFS was associated with baseline NETest activity in this cohort; median survival was 246 days (cut-off ≥80%) or 183 days (cut-off of ≥70%).

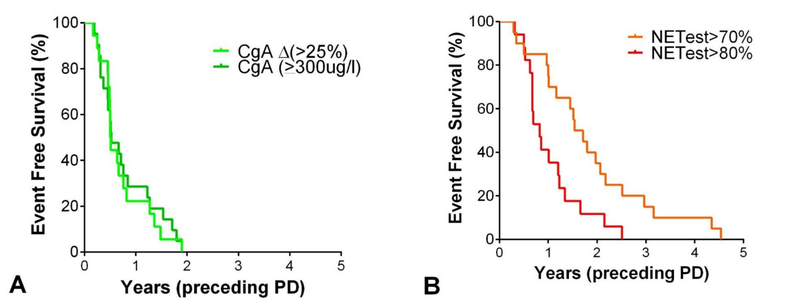

Figure 4
Time before blood-based biomarker elevations preceded image-based evidence for progressive disease.
4A) Changes in CgA (Δ25%) occurred at a similar time point (0.51 years) as an elevated CgA (≥300µg/l: 0.52 years) prior to image detected disease progression. Only fifty percent of patients (16 of 32) exhibited elevated CgA at baseline with a subset of ten exhibiting abnormally elevated (≥300ug/l) CgA.
4B) The median times prior to image-confirmed disease progression for the NETest were 0.82 years (≥80%) and 1.62 years (≥70%). All patients were NETest positive (>14%).

Conclusion

NETest correlated with well-differentiated GEP-NET clinical status. It identified clinically-actionable alterations ~1 year before image-based evidence of disease progression.

NANETs Jackson Hole, September 30, 2016