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

Wren Laboratories, Branford CT; Memorial Sloan Kettering Cancer Center, New York; Erasmus, Rotterdam, The Netherlands; Bad Berka, Bad Berka, Germany; UCL, London, United Kingdom; Warsaw; Poland; Charité - Berlin, Germany

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 I.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: Chi2, performance metrics analysis and progression-free survival (Kaplan-Meier).

Results
NETest was elevated in 175 (97%) vs CgA in 94 (52%) [X2=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 (R2=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% (X2=12.3, p<0.001). A low NETest (<40%) accurately predicted progression free survival and was significantly different (p=0.01, X2=6.57) compared to a NETest=40% (undefined v 253 days; HR=3.36. CgA was non-predictive (p=0.22).

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.

Figure 1: Concordance between imaging and NETest or chromogranin A (CgA). A: NETest was positive in 175 (97%) of subjects with histologically verified disease. CgA was elevated in 109 (60%) of subjects. B: CgA levels were normal in 100% of subjects with no evidence of disease (NED), five years after surgery. CgA levels were normal in all 12.

Figure 2: Metrics for NETest and CgA and NET-GEP disease. A: A positive NETest ≥2B had sensitivity, specificity and positive predictive value (PPV) >94% for GEP-NET disease. The negative predictive value (NPV) was 70%. B: For CgA, the specificity and PPV was 100% for an elevated measure (≥109ng/l). The sensitivity and NPV were ≤0%.

Figure 3: Concordance between imaging and NETest for identification of NET-GEP disease. For NETest, the specificity and PPV were ≥94% for a negative NETest. The sensitivity and NPV were ≤0%.

Figure 4: Disease status and biomarkers (baseline) NETest provides a sensitive measure of disease status at baseline. NET positive (≥14%) correlates with image-detected disease. A positive NETest correlated with clinical status (RECIST – stable or progressive disease) in 87% of cases. Elevated CgA correlated in 59% of cases. (p<0.02, bed 18). Metrics for NETest and CgA were 100% for sensitivity, specificity and NPV. NETest and CgA were all elevated (A). A NETest negative and CgA normal (B).

Figure 5: NETest predicts image-confirmed disease progression. NETest score at baseline predicted PFS in 77 patients. Patients underwent multiple different treatments (53% 4ZA, 27% 2STZ, 18% Zola-Durée). Elevated (≥12) associated with a median PFS of 253 days (6 months).

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