Circulating Neuroendocrine Gene Transcripts – the NETest – Accurately Identify GEP-NETs, Are Decreased by Surgery and Predict Tumor Progression and Recurrence

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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. We 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: 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 for 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).

Presented at NANETS 2016

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.