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Neuroendocrine Tumor Omic Gene Cluster Analysis Amplifies the Prognostic Accuracy of the NETest

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BACKGROUND: The NETest is a multi-gene assay comprising 51 circulating neuroendocrine tumor specific transcripts. The quotient of the 51-gene assay is based upon an ensemble of machine learning algorithms. Eight cancer hallmarks or "omes"(apoptome, epigenome, growth factor signalome, metabolome, proliferome, plurome, secretome SSTRome) represent 29 genes. The NETest is an accurate diagnostic (>90%) but its prognostic utility has not been assessed. In this study, we describe expansion of the NETest omic cluster components and demonstrate that integration amplifies NETest prognostic accuracy.

METHODS: Group 1 (n=222; including stable disease (SD: n=164), progressive disease (PD: n=76) and controls (n=139)). Group 2: NET Registry #NCT02270567 (n=88, prospective samples (SD n=54 and PD n=34) with up to 24 months follow-up. We used PubMed literature review, interactomic analysis, non-parametric testing, Kaplan-Meier survival curves and Chi2 analyses to inform and define the prognostic significance of NET genomic "hallmarks."

RESULTS: 2020 Analyses: In-depth analyses identified a further 6 omes: fibrosome, inflammasome, metastasome, NEDome, neurome and TFome. Group 1 analysis: Twelve omes were significantly ($p<0.05$, 2.1-8.2-fold) elevated compared to controls. In the PD group, 7 omes (proliferome, NEDome, epigenome, SSTRome, neurome, metastasome and fibrosome) were elevated versus SD. Group 2. All 7 omes were upregulated. In PD, they were significantly more elevated ($p<0.02$) than SD. The 7 omes exhibited a 69% prognostic accuracy; the NETest was 70.5% accurate.

A low NETest (<40) integrated with epigenome/metastasome was an accurate prognostic for PD (90%). A high NETest (>40) including the fibrosome/NEDome predicted PD development within 3 months (100%). Using decision tree analysis to integrate the 4 omes with the NETest generated an overall prognostic accuracy of 93%.

CONCLUSION: Five additional clinically-relevant cancer hallmarks were identified. Seven omic clusters provides a molecular pathological signature of disease progression. Integration of the epigome, fibrosome, metastasome, NEDome with the NETest score yielded 93% accuracy in the prediction of future disease status.

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