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# A Multi-Gene Transcript Blood Molecular Signature for Gut Neuroendocrine Tumors (NETs) Delineates Surgical Efficacy

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**Background:** Biomarker prediction of therapeutic efficacy is a key clinical index. A blood multi gene signature for gastroenteropancreatic neuroendocrine tumors (GEP-NETs) is a sensitive and specific biomarker for the detection of such neoplasia. Determination of tumor alteration in size is a key determinant of disease progress or regression. We propose that the extent of surgical cytoreduction should therefore be identifiable as a measure of therapeutic efficacy by blood gene transcript measurement and identify residual disease.

**Methods:** GEP-NETs (n=27) [M:F 14:13; age: 53 years, range: 37-74; stomach $n=1$, pancreas $n=8$, small intestine: $n=14$, appendix $n=3$, rectum $n=1$; G1=17, G2=10) were evaluated. There were ($n=10$) complete "R0" resections with 17 incomplete "R1/2" resections. Preoperative blood values and 1 month post-surgery were measured for 51 NET gene transcripts (GT) and CgA. A multianalyte algorhythmic analysis (MAAA) of RTPCR was used for the GT measurement and ELISA for CgA. Analyses included non-parametric paired testing and comparisons of MAAA and CgA as well as between R0 and R1/2.

**Results:** Surgical resection significantly reduced PCR scores (6.7±0.23 vs. 3.7±0.3, $p<0.0001$); no significant decrease was identified for CgA (58.5±32.5 vs. 55.2±36.5, $p=0.07$). R0 versus R1/2 comparison revealed that post-surgical PCR scores were significantly lower (2.8±0.4 vs. 4.1±0.4, $p<0.05$) following R0 resection. The R0 group was also associated with greater decreases in this score (-58±6.5% vs. -40±6.5, $p<0.05$). Although post-operative imaging identified disease in $n=1$ (10%) elevated gene scores were evident in 6 (60%) at 1 month. Two R0 individuals developed positive imaging at 6 months.

**Conclusion:** Surgical cytoreduction can be demonstrated by diminution of the peripheral blood NET gene transcripts. Values correspond with extent of resection. GT analysis identified residual disease in 60% of R0 resections. CgA measurement was unable to define the effect of surgery or identify residual disease. Application of a PCR-based blood test will facilitate assessment of completeness of surgical resection and early identification of residual/recurrent disease thereby increasing the therapeutic window of opportunity for other agents.