**Supplemental Material**

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

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**1. Supplemental Figures**

**1. Tumor location or grade and relationship to omes.**

An evaluation by tumor location (pancreatic vs. non-pancreatic) identified significant (*p*<0.05) differences in expression of the apoptome, fibrosome, GF-signalome and inflammasome (**Supplemental Figure 1A**). These were all upregulated in non-pancreatic NETs consistent with known pathobiological roles (1, 2). An evaluation by grade (G1/TC vs. G2/AC and G3), identified a significantly higher (*p*<0.05) apoptome in the higher grade tumors (**Supplemental Figure 1B**). This is consistent with the known correlation between increased an apoptosis and higher Ki-67 as has been previously described in lung and rectal NETs (3, 4).

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**1A**. **Tumor site**: Omic expression of the apoptome, fibrosome, GF-signalome and inflammasome were elevated in non-pancreatic NETs.

\**p*<0.05; \*\**p*<0.001

**1B**. **Histological grade**: Expression of the apoptome was increased in G2-G3 and AC tumors compared to G1/TC.

\**p*<0.05

**2. Prognostic comparison between Ki-67 and the NETest**

We evaluated the correlation between grade as assessed by Ki-67 or the number of omes and disease progression (**Supplemental Figure 2**). Ki-67 (G1/TC versus G2/AC) was associated with a hazard ratio of 1.47, which was not significant (*p*=0.37). In contrast, patients with >3 omes exhibited a median PFS of 6 months and was associated with a hazard ratio of ~4 as a prognostic. The prognostic accuracy of omes alone was ~70% which was better (*p*=0.07) than for Ki-67 which was 58%.



**2A-B. Survival Curves in Cohort II.**

Kaplan-Meier survival curves were generated for Ki-67/grade (2A) and NETest (2B). For grade, we compared G1/TC versus G2/AC. While this was associated with a median progression free survival (mPFS) of 10 months in high grade lesions vs. not reach for G1/TC tumors, the hazard ratio was 1.47 with a non-significant Chi2 (0.8, *p*=0.37). For NETest, we evaluated low versus high scores (<40 vs. >40). The NETest was associated with significant differences (Chi2 = 43.12, *p*<0.0001) in outcomes: mPFS = 3 months vs. not reached. This demonstrates that the NETest (using low vs. high cut-off) provides highly significantly prognostic information.

**2C-D. Accuracy of prediction.**

Using Ki-67/grade, the prognostic accuracy was 58% (for G1/TC and for G2/AC) with an overall accuracy of 58% (37/64). For the NETest, a low score was 65% accurate, a high score was 85% accurate, and overall, the prognostic accuracy was 70.5%. A comparison between the NETest and Ki67 identified this trended toward significance (*p*=0.07, Fisher’s test).

**3. Clinical implication of NETest and novel omes**

The clinical applications of the NETest are illustrated in **Figure 7 (main text)**.

The first clinical utility is as a biomarker for tumor status (stable or not at the time of blood draw). This has fundamental importance for defining e.g., whether a patient is responding to therapy or, if they are in a watch-and-wait program, whether they require treatment intervention. Under these conditions, the NETest can be used as a dynamic (e.g., every 3 months) measurement of clinical behavior.

The second utility relates to those specifically with a low score (<40). A proportion (~ one third) of these patients will progress and it would be clinically beneficial to predict those in who this would occur. Integration of the epigenome/metastasome (prognosome) data into a low score accurately identified (>90%) those who progressed at an early stage. Early intervention is a critical component of clinical management and identification of this is important given the known difficulties with morphological assessment of slow-growing tumors (5).

**4. Biological validation of novel omes**

**Fibrosome:** This included *APLP2*, *BNIP3L*, *CD59, CTGF*. APLP2 is evident in cardiac fibrosis (6) and BNIP3L reported to promote cardiac fibrosis through TGF-pathway activation (7). Complement dysregulation via CD59 has also been identified to play a role (8), while CTGF is a well-known profibrotic factor (9). The fibrosome has been independently been demonstrated to be an effective blood-based tool to detect fibrosis in NETs (1).

The ***inflammasome*** was not significantly upregulated in NETs compared to controls but was increased in non-pancreatic vs. pancreatic NETs. Genes included *CD59, PHF21A, PQBP1,* and *SMARCD3.*

**Metastasome:** This signature comprises 7 genes, three of which overlap with the fibrosome – *APLP2*, *CD59* and *CTGF*. The other 4 genes included *ARHGEF40* (FLJ10357 or Solo) which is a RhoA-targeting guanine-nucleotide exchange factor involved in mechanical force-induced RhoA activation and stress fiber formation which regulate cell movement (10). Similarly, *NUDT3* functions as an mRNA decapping enzyme that orchestrates a subset of mRNAs to modulate cell migration (11). *COMMD9* is directly involved in cell migration in non-small cell lung cancers in a TFDP/E2F1-dependent manner (12). *ATP6V1H* plays a role in bone dynamics and remodeling (13).

**NEDome**: This comprises 21 genes, 10 of which overlap with the neurome (see **Table 2, Figure 2**). This was identified as the “C4” signature by Chen and colleagues (14) and was detectable in tissue from CNS tumors and associated with poor prognosis in tumors (including adenocarcinomas) with a neuroendocrine genotype (14). The independent large data set of Chen *et al*., supports the proposal that the NEDome represent a relevant signature of NET pathology and may be relevant to predicting outcome. In our original transcriptomic NETest pipeline, we did not exclude genes from CNS malignancies (15). Thus, the identification that NECome genes in CNS malignancies suggests that the NETest may identify not only NETs but tumors that have a more dominant neural phenotype. This proposal is supported by the fact that the NETest identifies paragangliomas and pheochromocytomas with a high degree of accuracy (100%) (16).

**Neurome:** The neurome included 17 genes (one third of the target genes in the NETest) previously associated with neuroendocrine disease like *APLP2*, *ENPP4*, *TPH1*, *VMAT1/2* etc. (14, 17, 18).

**TFome:** This included three transcription factors, *ZFHX3*, *ZXDC* and *ZZZ3* all reported to be functionally effective especially in neuronal tissue and inflammation (19-21).

**5. References**

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