BACKGROUND AND SIGNIFICANCE
- Pancreatic Neuroendocrine Tumors (PNETs) represent neoplasms with heterogeneous behavior and presentation, resulting in a paucity of generalizable molecular data.
- Present studies limited by single-institution analyses and small sample size.
- Using publicly-available datasets, we established a large, multi-institutional cohort of patients for analysis.
- Patients with known neuroendocrine carcinoma were excluded.
- Genes with somatic mutations and available clinical data were analyzed. Genes mutated at <5% frequency were not included for analysis.
- For patients with multiple samples, tumor with the highest TMB was used as the representative sample.

METHODS
- The following publicly-available genomic datasets were queried via cBioPortal: MSK-IMPACT, MSK-MET, MSK-PANET 2023, PCAWG, ARC-NET, Origami, JHU PANET, Insulinoma Shanghai, and MET500.
- Significance testing was done by Mann-Whitney U for central tendency, Chi-square or Fisher’s exact for association, Wald for logistic regression, and logrank for survival.
- Statistical testing by association performed using Wilcox Rank Sum Test.
- Statistical testing by Fischer’s Exact test.
- Statistical testing by logrank.
- For patients with at least 5% mutational frequency, statistical testing by Fisher’s Exact test.

RESULTS
- ATRX and DAXX mutations are associated with Nodal Involvement.
- Compared to ATRX/DAXX wild-type metastatic disease, ATRX/DAXX mutant metastatic disease demonstrates wider distribution of survival.
- ATRX and/or DAXX mutations are associated with regional nodal involvement.
- Statistical testing by Fisher’s Exact test.

SUMMARY
- Largest aggregate landscape of somatic mutations of PNETs utilizing multiple publicly-available datasets.
- ATRX and DAXX mutations are mutually exclusive in primary tumors, exhibiting loss of convergence on these same pathways.
- DAXX mutations demonstrate co-occurrence with both ATRX and ATRX mutations separately.
- TP53 and KRAS mutations correlate with aggressive disease.
- ATRX and DAXX are nearly mutually exclusive in primary tumors and loss this mutual exclusivity in metastatic lesions, implicating their shared molecular pathway.
- ATRX/DAXX mutations correlate with regional but not distant disease and correlate with improved survival in those with ATP5A1/DAXX-mutated metastatic disease.
- In the subset of patients with available correlative clinical data, regional nodal involvement does not correlate with a decrement in survival.
- TP53 mutations are highly correlated with metastases and co-occur with KRAS mutations, both mutations are associated with poor overall survival, possibly indicating a unique tumor subgroup of aggressive disease.