Title: Germline Pathogenic/Likely Pathogenic (P/LP) Variants in Epithelial Neuroendocrine Neoplasms: The Case for Universal Germline Genetic Testing

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Background: Current National Comprehensive Cancer Network (NCCN) guidelines for germline testing in neuroendocrine neoplasms (NENs) rely on organ-specific, syndrome-driven algorithms that may not adequately capture hereditary risk. We sought to analyze prevalence of P/LP germline variants in epithelial NENs and investigate relevant associations.

Methods: Germline genetic testing results were analyzed from 3,611 probands. Cohort 1 included 3,409 patients identified by ICD-10 code C7A (2015–2025), and Cohort 2 included 201consecutively curated patients with pathology information (2019–2021). Patients with paraganglioma, pheochromocytoma, or medullary thyroid carcinoma were excluded. Except 59single-gene tests, multigene panels included a mean of 67 and 62 genes in Cohorts 1 and 2,respectively. Data were classified as P/LP, variant of uncertain significance (VUS), or negative. Comparisons of variant classification frequencies between cohorts were performed using chi-square or Fisher's exact tests. Multivariable logistic regression evaluated clinical and demographic predictors of P/LP variant detection, with results reported as likelihood ratios (LR)and two-sided p-values (< 0.05 considered significant).

Results: Among all 3,611 probands, mean age was 56 years in Cohort 1 and 53 years in Cohort 2, with females comprising 63% and 71%, respectively. VUS and negative results differed between cohorts (VUS 21.9% vs 32.9%, $p = 0.002$; negative 67.4% vs 55.0%,$p < 0.001$), while P/LP rates were similar (10.6% vs 12.1%, $p = 1.0$), permitting pooled analysis. Overall, 387 patients (10.7%) harbored P/LP variants, with 399 P/LP variants identified across49 genes. Sixty percent of P/LP variants were accounted for by *CHEK2, MEN1, BRCA2, ATM,FH, HOXB13, PALB2,* and *BRCA1*. Clinically actionable variants per NCCN guidelines were identified in 348 patients (9.6%). Among 479 probands with curated family history, meeting NCCN criteria for multigene testing or having a family history of NEN was not predictive of P/LP detection. Logistic regression demonstrated that male sex was a significant predictor of P/LP variants (LR = 4.538, $p = 0.03$), while age at NEN diagnosis and primary NEN site were not predictive, nor were the interaction terms significant.

Conclusions: In this 10-year, multicohort study of patients at a commercial laboratory, more than one in ten patients with epithelial NENs harbored a germline P/LP variant, frequently outside classic hereditary NEN syndromes and inadequately predicted by NCCN criteria, family history, age, or tumor site. These findings suggest that current germline testing frameworks may miss clinically relevant hereditary cancer risk. Broader approaches to germline testing in these patients may be needed to improve identification of hereditary cancer risk and enable personalized prevention and surveillance strategies.