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Emerging Value of Multigene Panels for Germline Testing in Patients with Neuroendocrine Tumors

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BACKGROUND: Neuroendocrine tumors (NETs) are known to be associated with hereditary syndromes stemming from MEN1, VHL, SDH or TSC mutations. Recent data suggest that additional germline mutations may be relevant, implying a role of germline testing with multigene panels. We examined genetic counseling (GC) referral and testing patterns, test results, and their changes over time in NET patients.

METHODS: Retrospective chart review was conducted in 236 NET patients referred to UCSF Cancer Genetics and Prevention Program 2004-2017. Univariate logistic models were used to assess relationship between binary outcomes and covariates. STATA was used for analysis and statistical significance was based on $p < 0.05$.

RESULTS: 139 referred patients (59%) followed up with GC. Patients with >1 family members diagnosed with cancer were more likely to attend GC [OR=2.75, p=0.010]. Among 107 patients tested, small bowel NETs were less associated with genetic testing than pancreatic NETs [OR=0.15, p=0.001]. Single-gene tests were routine until 2015, when panels up to 130 genes became standard. Overall, 31 patients (29% of 107 tested) had a pathogenic/likely pathogenic (P/LP) result. There was no significant difference between single and multi-gene tests in identifying P/LP mutations (likely due to changes in threshold for testing over time), but greater diversity in P/LP mutations was noted with larger panels. Functional tumors showed a lower rate of P/LP mutations than non-functional tumors [OR=0.17, p=0.037].

CONCLUSION: Only 59% of referred patients followed up with GC, suggesting that significant barriers to testing exist. Of those tested, 29% harbored a P/LP mutation. Germline mutations not traditionally associated with NETs were identified, highlighting the potential importance of larger panels to detect rare mutations.

Table 1:

Germline mutations by tumor type, n (%)

Total (n=31)	Pancreas (n=11)	Paraganglioma/ pheochromocytoma (n=8)	Small Bowel (n=1), Other NET (n=9) & Unknown Primary (n=2)
MEN1, 11 (35%)	8 (73%)		3 (25%)
SDHB, SDHC or SDHD, 9 (29%)		7 (88%)	2 (17%)
FLCN, 1 (3%)			1 (8%)
MUTYH, 2 (6%)	2 (18%)		
APC, 2 (6%)	1 (9%)		1 (8%)
MLH1 or MSH6, 2 (6%)			2 (17%)
CHEK2 or PALB2, 2 (6%)			2 (16%)
BLM, 1 (3%)			1 (8%)
FANCC, 1 (3%)		1 (12%)	