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Genetic Predisposition Testing Program for Pancreatic Neuroendocrine Neoplasms (PanNENs): Interim Analysis of a Multicenter University of California Cohort

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BACKGROUND

Previous reports suggest pathogenic/likely pathogenic germline variants (P/LPVs) occur in ~20% of patients with PanNENs, but the downstream consequences remain incompletely defined; data from diverse populations are limited. Previously presented as a Trial-in-Progress at NANETS 2024 (Abstract ID 28698), we report the first interim analysis of an ongoing study.

METHODS

This multicenter observational study (IRB#22-37899) includes University of California sites in San Francisco (UCSF), Los Angeles (UCLA), and San Diego (UCSD). Accrual is complete at UCSF and UCSD, with enrollment ongoing at UCLA. New and existing patients with PanNENs were eligible (any stage). Prior dedicated germline testing and on-study testing were included; patients without prior large-panel testing (>80 genes) were offered UCSF's Expanded Hereditary Cancer Panel (88-97 genes). The primary objective was the frequency of P/LPV germline variants.

RESULTS

Among 215 enrolled patients at UCSF and UCSD, 131/215 (61%) had prior germline testing (any panel size). Overall, 117/215 (54%) were male, the median was age 56 (32% , and 125/215 (58%) with locoregional disease. Most patients identified as White 143/215 (67%), 37/215 (17%) Hispanic or 28/215 (13%) as Asian.

Results are available for 203/215 (94%) participants. Among these, at least one P/LPV identified in 44/203 (22%). Most (41/44, 93%) had well-differentiated tumors; differentiation was unknown in 3/44 (7%). Tumors were grade 1/2 in 40/44 (91%), G3 in 1/44

(2%), and unknown in 3/44 (7%). Overall, 14/44 (32%) , 41% female; 7/44 (16%) identified as non-White, 3/44 (7%) as Hispanic. P/LPVs included MEN1 (8), MUTYH (7), CHEK2 (5), and pancreatitis-associated genes CFTR (9) and SPINK1 (2). Additional P/LPVs were noted in BRCA1, BRCA2, NBN, ERCC4, LZTR1, PALB2, RINT1, TP53, and TSC1. Variants of uncertain significance (VUS) identified in 118/203 (58%). Of decision survey respondents, 93/95 (98%) agreed or strongly agreed that pursuing genetic testing was the right decision.

CONCLUSIONS

P/LPVs were identified in genes associated with hereditary endocrine neoplasia, DNA repair, or pancreatitis. P/LPVs spanned high-, moderate-, and low-penetrance alterations (including carrier status) in addition to VUS, underscoring the complexity of germline testing in this population. Our cohort is relatively diverse, providing new insight into Hispanic and Asian subgroups. Participants reported high satisfaction with their decision to undergo genetic testing. Accrual is still ongoing at UCLA (total target N=300). Information regarding the consequences of P/LPVs will be reported in future analyses (e.g. impact on tumor pathogenesis, cascade testing, screening recommendations, and second cancers).

ABSTRACT ID #36536