UCSF Helen Diller Family Comprehensive Cancer Center

Analysis of patient selection for germline testing in early-onset gastroenteropancreatic neuroendocrine neoplasms (GEPNENs) at a single institution

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Background

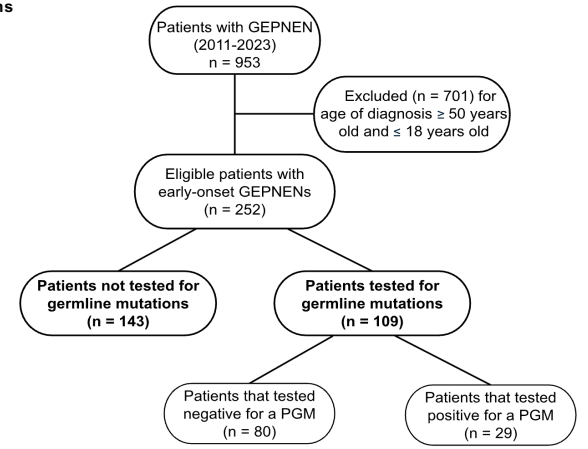
- Our prior work demonstrated a notable rate of pathogenic or likely pathogenic germline mutations (PGMs) among patients diagnosed with early-onset gastroenteropancreatic neuroendocrine neoplasms(EO-GEPNENs) at UCSF, particularly of pancreas primary.[1]
- Despite these findings, no uniform standards currently exist for germline testing in EO-GEPNENs.[2]
- Germline testing in patients with pancreatic NENs typically hinges on provider workflow, clinical presentation, patient interest or willingness, and insurance coverage.[3]
- This case-by-case approach relies on subjective provider judgment rather than objective criteria, potentially leading to unequal access to testing.
- The present study aims to compare the clinicodemographic features of EO-GEPNEN patients to better understand current practice patterns and inform future guidelines.

Methods

- Retrospective IRB-approved cohort
- Eligible patients include age 18 to < 50 at diagnosis of GEP-NEN between 2011-2023, any stage, any grade, and regardless of functional status or family history
- Chi-squared tests and Wilcoxon rank sum tests were used to test associations for clinicopathological features by germline testing.
- Assessed who underwent germline testing using a dedicated germline panel or analysis of tumor/normal samples through somatic tumor mutation profiling
- Penetrance – High (relative risk (RR) >5), Moderate = RR 2-5, Low (RR < 2) or uncertain (x) penetrance based on the highest reported risk in any cancer type
- "Hereditary pattern" = clinical diagnosis of a genetic cancer syndrome
- "Suspected genetic syndrome" = hereditary pattern and/or first-line family members with a cancer diagnosis
- "Recs" = genetic counseling recommendations after germline testing

Results

Figure 1: CONSORT diagram depicting patients with EO-GEPNENs tested for germline mutations

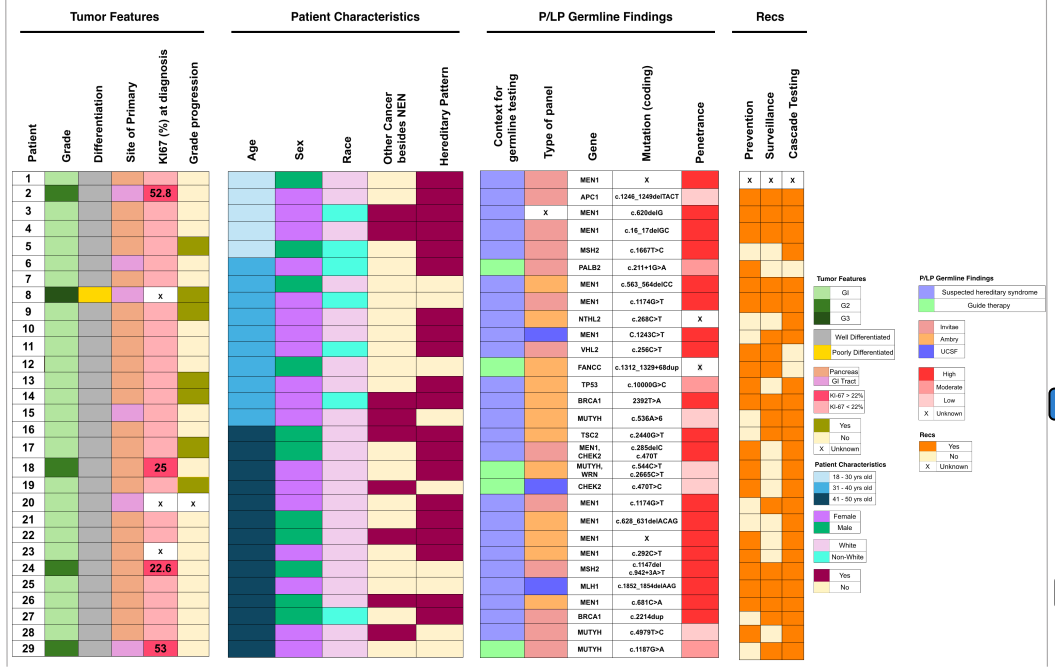


Results

Table 1: Clinicopathologic features of patients with EO-GEPNENs that were tested for germline mutations

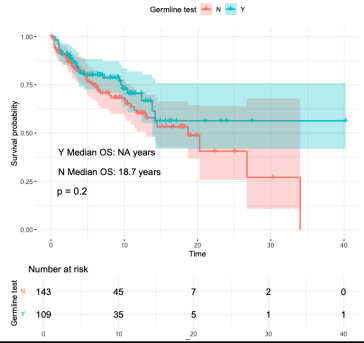
Characteristic	Overall (n = 252, 100%)	Not Tested (n=143, 56.7%)	Tested (n=109, 43.3%)	P Value
Age (mean (SD))	40.3 (7.4)	40.5 (7.0)	40.2 (7.8)	0.752
Sex				
Male	114 (45.2)	65 (45.5)	49 (45.0)	1
Female	138 (54.8)	78 (54.5)	60 (55.0)	
Race				
White	168 (66.7)	86 (60.1)	82 (75.2)	
Non-White	66 (26.2)	43 (30.1)	23 (21.1)	**0.027**
Unknown	18 (7.1)	14 (9.8)	4 (3.7)	
Hereditary pattern	31 (12.3)	10 (9.2)	21 (19.3)	**<0.001**
Other Cancer besides NEN	32 (12.7)	10 (7.0)	18 (16.5)	0.267
Primary Tumor Site				
GI	120 (47.6)	70 (49.0)	50 (45.9)	0.721
Pancreas	132 (52.4)	73 (51.0)	59 (54.1)	
Grade at Diagnosis				
G1/G2 NET	190 (75.4)	108 (75.5)	82 (75.2)	
G3 NET	15 (5.9)	3 (2.1)	12 (11.0)	**0.014**
G3 NEC	14 (5.6)	8 (5.6)	6 (5.5)	
Unknown	33 (13.1)	24 (16.8)	9 (8.3)	
Metastatic Disease	161 (63.9)	79 (56.4)	82 (75.2)	**0.003**

Figure 2: Summary of tumor features and germline testing indications, results, and downstream implications for EO-GEPNEN patients with P/LP germline variants. Patients are sorted by age.



Results

Figure 3: Kaplan-Meier curve of patients with EO-GEPNENs that were tested or not tested for germline mutations



Conclusions

- 43.3% (n=109) of 252 patients with EO-GEPNENs underwent germline testing.
- 26.6% of tested patients had a pathogenic germline mutation (PGM), including 14% with GI and 37% with pancreatic primaries.
- The tested group was enriched for White race (p=0.027), a suspected hereditary pattern (p<0.001), G3 tumors, and stage IV disease, likely reflecting routine tumor mutation profiling (tumor/normal pair) in this population.
- No significant differences were observed in age, sex, or primary tumor site between tested and non-tested patients.
- These findings suggest potential racial disparities in germline testing, though it remains unclear whether this stems from differences in patient selection, access, or other systemic barriers.
- Overall survival was similar between tested and non-tested groups.
- Tested patients with EO-GEPNENs had a high rate of PGMs, underscoring the need for a consensus on germline testing guidelines in this population.
- Most patients with PGMs had another cancer besides NEN or evidence of a suspected hereditary syndrome (hereditary pattern and/or first-degree family members with cancer).
- All identified PGMs led to downstream clinical actions, including enhanced screening, prevention, or cascade testing.
- Limitations: retrospective study design, relatively small sample size, lack of a uniform testing panel, and absence of tumor mutation data to determine if PGMs were incidental or causative.
- Future directions: clarify indications for germline testing in EO-GEPNENs based on clinicodemographic and tumor features (including race and grade) and assess the clinical implications of testing outcomes.

References

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2. Nadine Tung et al. Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline. *J Clin Oncol* **42**, 2599-2615(2024)
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