Comparison Of Germline Pathogenic Variant Rates In Unaffected Individuals With Second-Degree Versus First-Degree Relatives With Pancreatic Cancer

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Background

- Individuals diagnosed with pancreatic cancer (PC) have a higher likelihood of testing positive for a pathogenic variant (PV) in genes associated with PC.
- In 2018, the National Comprehensive Cancer Network® (NCCN®) recommended germline testing for all individuals with PC and their unaffected first- and second-degree relatives (FDR and SDR).[1]
- In 2019, these guidelines limited testing to only FDR of individuals with PC.[2]
- PC screening is currently recommended for PV carriers of *STK11, CDKN2A, ATM,* and *BRCA2,* regardless of family history, and for PV carriers of *BRCA1, PALB2,* Lynch, and *TP53* with family history.[3]

OBJECTIVE: This study evaluated the PV rate for individuals unaffected with cancer, with either an FDR or SDR diagnosed with PC, who were referred for hereditary cancer testing.

Methods

- The study included individuals who had multigene pan-cancer germline testing (25 to 48 genes) between September 2013 and September 2024.
- **Individuals were separated into three cohorts for comparison:**
  - A personal history of PC and no family history of PC (proband)
  - No personal history of PC and an FDR with PC
  - No personal history of PC and an SDR with PC
- **Individuals were excluded if they had either:**
  - A personal or family history of other cancers
  - Both an FDR and SDR with PC

Table 1. Demographics of PC cohorts

	Proband with PC	FDR with PC	SDR with PC
Total (n)	**2153**	**2803**	**1531**
Reported Sex, %			
F	46	85	92
M	54	15	8
Age at Testing			
Range*	23 - “90 or older”	18 - 85	18 - 72
Median	65	50	40
Diagnosis Age of PC			
Range	“under 18” to “90 or older”	“under 18” to “90 or older”	“under 18” to “90 or older”
Median	64	63	65

*Individuals under 18 years of age at the time of testing were excluded from the study. However, diagnoses under 18 are included in this data.

Results

- The three PC cohorts are described in **Table 1**.
- The PV rates observed in the proband history, FDR, and SDR cohorts are 10.0%, 7.4%, and 6.4%, respectively (**Table 2**).
- Excluding monoallelic *MUTYH,* the highest prevalence of PVs were identified in the following genes (indicated with asterisks in **Figure 1**):
  - *BRCA2, ATM,* and *PALB2* in the proband history cohort
  - *ATM, BRCA2,* and *CHEK2* in the FDR cohort
  - *ATM, CHEK2,* and *BRCA2* in the SDR cohort
- There was a marked increase in those with a SDR with PC undergoing germline testing in 2019, followed by a decline, aligning with changes in NCCN Guidelines® (**Figure 2**).[1]

Table 2. PV rates by personal/family history of PC

	Proband with PC	FDR with PC	SDR with PC
Total PVs, including carriers, n (%)*	**10.0%** (216)	**7.4%** (208)	**6.4%** (98)
Total PVs, excluding carriers, n (%)*	**8.1%** (175)	**5.4%** (152)	**4.6%** (71)
Total PVs in pancreatic genes, n (%)**	**5.9%** (128)	**3.2%** (90)	**2.4%** (36)

*Carriers defined as mono-allelic *MUTYH, MSH3,* or *NTHL1* or heterozygous FH c.521C>G or c.1431_1433dup
**Pancreatic genes: *ATM, BRCA1, BRCA2, CDK4, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53*

Figure 1. PV gene distribution by personal/family history of PC

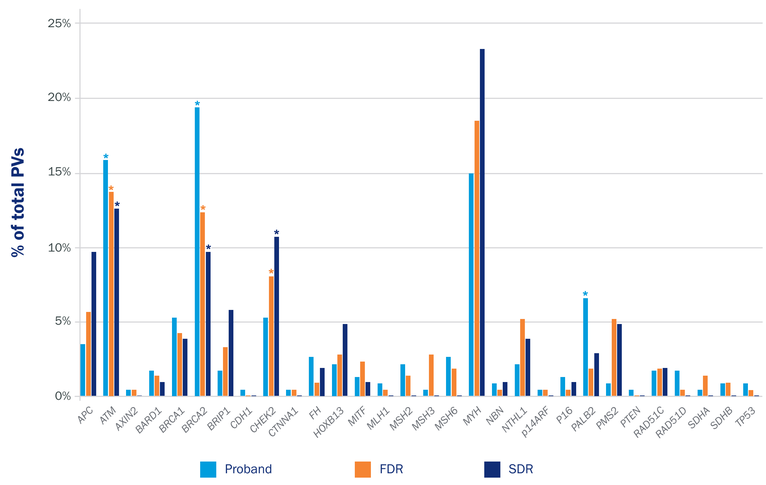
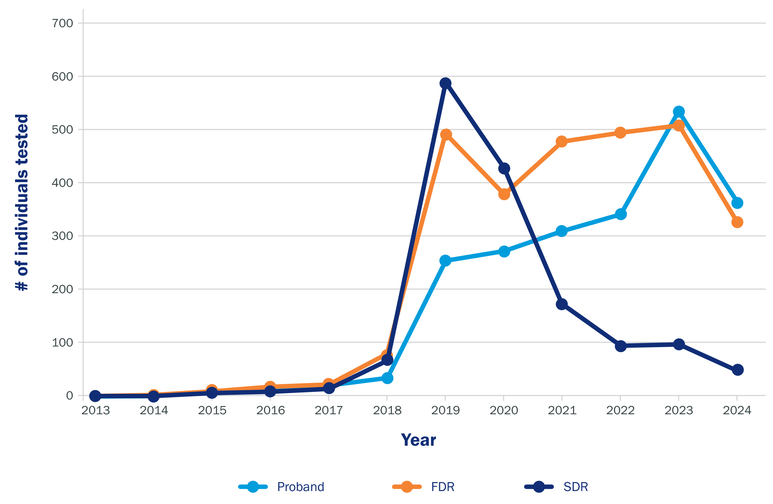


Figure 2. Trend in germline testing by personal/family history of PC by year tested



*Excluding monoallelic *MUTYH* (aka MYH), the three genes with the highest prevalence of PVs in each cohort

Conclusions

- The similar PV rate in unaffected individuals with a first- or second-degree relative with PC supports the NCCN germline testing guidelines published in 2018, which includes those with a second-degree relative diagnosed with PC.[1]
- Existing testing guidelines may fail to identify approximately 2% of unaffected individuals with a SDR diagnosed with PC who carry PVs in PC-related genes, resulting in missed opportunities for screening within this population.

References: Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: **(1)** Breast and Ovarian. V1.2019; Genetic/Familial High-Risk Assessment: **(2)** Breast, Ovarian, and Pancreatic. V1.2020. Dec 4, 2019; **(3)** Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate. V 3.2025. All rights reserved. Accessed March 6, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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