

Survival and treatment trends in BRCA-mutated metastatic pancreatic adenocarcinoma

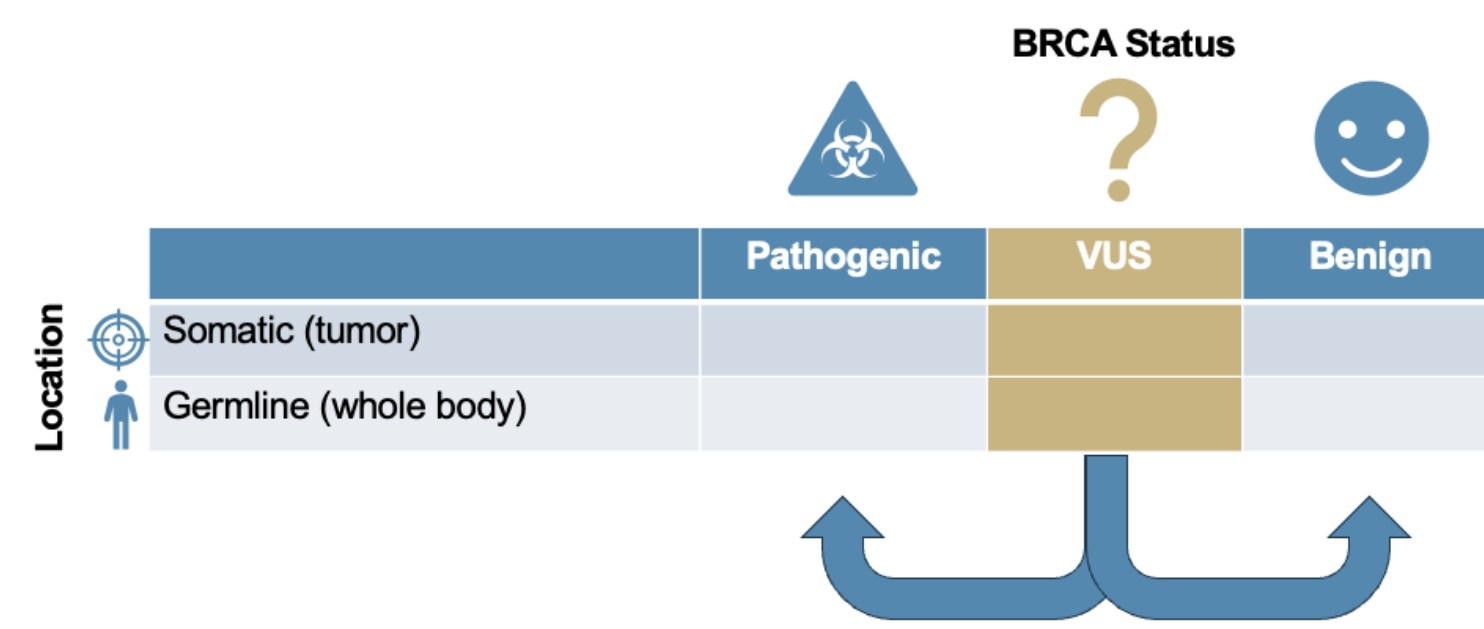
Abstract: 518208

Gabriel Haw, Vida Alami, Junxiao Hu, Wells A. Messersmith, Alexis D. Leal, Sunnie S. Kim, Hannah R. Robinson, Emily Baiyee Toegel, Christopher H. Lieu, S. Lindsey Davis



Background

- Pancreatic ductal adenocarcinoma (PDAC) is associated with a poor prognosis, with five-year survival of 8% across all stages (exocrine tumors only, ACS Cancer Facts 2025).
- Germline pathogenic mutations in the Homologous Recombination Repair pathway - including BRCA1/2, among others - result in a higher risk of developing PDAC, as well as increased sensitivity to cytotoxic, platinum-based chemotherapy and PARP inhibitors.
- This increased sensitivity has been established across multiple primary tumors, highlighting a shared, exploitable relationship between systemic, DNA-damaging therapies and dysfunctional DNA repair.
- The POLO III trial established a progression free survival benefit to the use of PARP inhibitors as maintenance therapy in patients with germline-pathogenic BRCA mutations with metastatic pancreatic cancer. Real-world treatment trends since this trial are not fully characterized.
- The impact of somatic-pathogenic BRCA mutations, as well as somatic and germline Variants of Uncertain Significance (VUS), on PDAC outcomes are also not well characterized.



Methods

- The Flatiron Health Research Database (FHRD) contains de-identified patient-level data originating from over 280 cancer clinics in the United States. Patients with metastatic PDAC and BRCA testing were included.
- Using patient-level data from the FHRD collected between 2017 and 2024, we conducted multivariate analyses to evaluate the association of BRCA mutations with survival outcomes and treatment patterns in metastatic pancreatic cancer patients.
- BRCA mutated tumors in the context of demonstrated pathogenic germline mutations were considered germline. Biomarker test definitions differed based on the specific aim being considered – as below.

Table 1: Select Patient Demographics and Genotype Frequencies

FHRD Designation (Ever Positive)		Benign	Germline Pathogenic	Germline VUS	Somatic Pathogenic	Somatic VUS	Total
Total (%)		2407 (86.0)	103 (3.7)	40 (1.4)	101 (3.6)	149 (5.3)	2800 (100)
Sex (%)	F	1157 (48.1)	49 (47.6)	18 (45.0)	37 (36.6)	68 (45.6)	1329 (47.5)
	M	1250 (51.9)	54 (52.4)	22 (55.0)	64 (63.4)	81 (54.4)	1471 (52.5)
Age	Median (IQR)	68.0	64.0	66.0	67.0	70.0	68.0
Age Range	Range	62.0 - 75.0	57.0 - 71.5	59.0 - 74.5	62.0 - 74.0	62.0 - 75.0	61.0 - 75.0

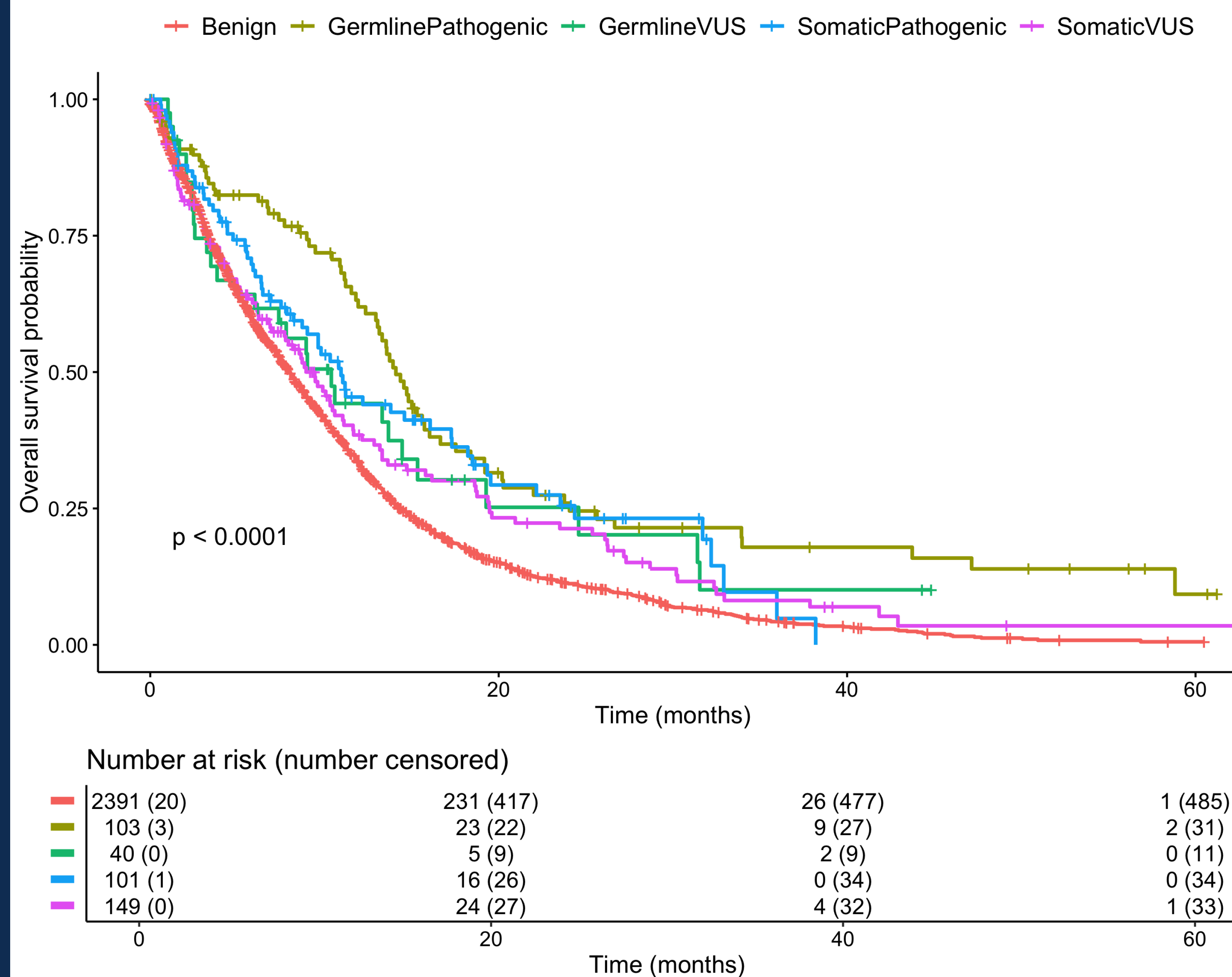


Figure 1: Kaplan – Meier Survival Curve for Genotype Groups. Germline and somatic pathogenic mutations, as well as Somatic VUS, in the genes BRCA1 and BRCA 2 were independently associated with improved overall survival.

- Germline pathogenic carriers also exhibited a longer time to next treatment (TTNT).
- No differences in first line platinum use were detected.
- Germline pathogenic carriers had a higher likelihood of receiving more lines of therapy.
- Five year survival from time of metastatic diagnosis approached 0.

We would like to acknowledge Flatiron Health for their assistance on this project.

Results

Table 2: OS Testing results (Mutation Status Defined with Ever Positive Framework)

Mutation	Median (months)	HR – Multivariable Cox Proportional Hazard
Benign	8.05	-
Germline Pathogenic	14.14	0.56 (0.43-0.73, p<0.001)
Germline VUS	10.42	0.78 (0.51-1.19, p=0.250)
Somatic Pathogenic	10.98	0.61 (0.45-0.81, p=0.001)
Somatic VUS	9.47	0.80 (0.64-0.99, p=0.041)

Table 3: TTNT Testing results (Mutation Status Defined with Ever Positive Framework)

Mutation	Median (months)	HR – Multivariable Cox Proportional Hazard
Benign	4.8	-
Germline Pathogenic	6.35	0.74 (0.60-0.93, p=0.008)
Germline VUS	6.02	0.75 (0.53-1.05, p=0.096)
Somatic Pathogenic	4.73	1.00 (0.81-1.22, p=0.983)
Somatic VUS	4.57	0.93 (0.78-1.10, p=0.389)

Table 4: Treatment Dynamics (Mutation Status Defined at Index Date)

Mutation	Plat 1 line – No (%)	Plat 1 line – Yes (%)	OR 1 st Line Platinum - Multivariable Logistic Regression	OR – therapy# - Multivariable Brant Wald Proportional Odds
Benign	410 (88.9)	339 (86.0)	-	-
Germline Pathogenic	12 (2.6)	21 (5.3)	1.35 (0.63-2.98, p=0.445)	2.42 (1.29-4.49, p=0.006)
Germline VUS	3 (0.7)	6 (1.5)	3.03 (0.77-14.74, p=0.127)	1.41 (0.37-4.63, p=0.582)
Somatic Pathogenic	25 (3.3)	16 (4.1)	0.92 (0.42-1.99, p=0.824)	1.13 (0.53-2.11, p=0.744)
Somatic VUS	21 (4.6)	12 (3.0)	0.76 (0.35-1.61, p=0.489)	1.10 (0.54-2.11, p=0.778)

- In a post-hoc analysis, the use of platinum-based chemotherapy in the first line was found to not moderate or mediate the effect between BRCA status and OS, however it was a significant covariate for overall survival and was therefore included in the final multivariable analyses.

Future Directions for Research

- Prospective studies are needed to further elucidate the behavior of somatic-pathogenic BRCA-mutated PDAC.
- The demonstrated survival benefits without changes in platinum in the first line may be due to introduction in subsequent lines, or the effect of other targeted therapies. Characterization of this was limited by a smaller sample size.
- Further differentiation of BRCA VUS will help guide targeted therapy, as a subset of VUS do appear to have survival trends more similar to pathogenic variants.