Supplementary Table 1. Criteria for Referral of PDAC patients to Genetic Counseling in the HRC

REFERRAL CRITERIA
• Patients younger than 60 years old. • Personal history of breast cancer, ovarian cancer or melanoma. • Family history of pancreatic cancer • Family history of breast cancer at age < 50 or ovarian cancer or melanoma at age <40. • Family history of a known mutation for a cancer predisposition syndrome

Supplementary Table 2. Comparison of Demographical Information, Clinical Characteristics, and Family History of Cancer between PDAC patients tested and non–tested patients in the HRC.

Characteristic	Tested (n=277)	Non-tested (n=307)	p-value
Mean (range) age at diagnosis, years	60.3 (28-89)	62.6 (25-87)	**0.019**
Sex			
Female	149 (53.8)	161 (52.4)	0.803
Male	128 (46.2)	146 (47.5)	
Race			
White	235 (84.8)	248 (80.7)	
Hispanic	19 (6.8)	21 (6.8)	0.167
Black	13 (4.7)	29 (9.4)	
Asian	10 (3.6)	8 (2.6)	
Unknown	0	1 (0.3)	
Risk Factors			
Smoking History			
Never	173 (62.5)	167 (54.3)	0.053
Past/Current	104 (37.5)	140 (45.6)	
Alcohol History			
Never	94 (33.9)	124 (40.3)	0.123
Occasional/Heavy	183 (66.0)	183 (59.6)	
History of Pancreatitis	17 (6.1)	37 (12.0)	**0.014**
Chronic Diabetes	38 (13.7)	58 (18.8)	0.095
New-Onset Diabetes	34 (12.2)	45 (14.6)	0.467
Personal History of Cancer			
Breast	56 (20.2)	24 (7.8)	**0.0001**
Gynecologic	19 (6.2)	7 (2.2)	**0.0085**
Melanoma	9 (3.2)	4 (1.3)	0.1595
Colon	14 (5.1)	11 (3.5)	0.4179
Family History of Cancer			
≥1 affected FDR			
Breast	97 (35)	74 (24.1)	**0.0047**
Pancreas	63 (22.8)	64 (20.8)	0.6160
≥1 affected SDR			
Breast	86 (31)	80 (26.0)	0.1987
Pancreas	57 (20.5)	54 (17.5)	0.3985

Supplementary Table 3. Mutation nomenclature and classification found in the early-onset PDAC patients from HRC (Age <60).

	Germline Mutation				
PIN	**gene**	**type of mutation**	**cDNA**	**protein**	**Classification**
M1	STK11	deletion	deletion exon 1	p.?	Pathogenic
M2	BRCA2	duplication	c.3264dup	p.Gln1089Serfs*10	Pathogenic
M3	BRCA1	small deletion	c.5530del	p.Leu1844Serfs*11	Pathogenic
M4	BRCA2	small deletion	c.5946del	p.Ser1982Argfs*22	Pathogenic
M5	BRCA2	small deletion	c.778_779del	p.Glu260Serfs*15	Pathogenic
M6	BRCA1	duplication	duplication exon 13	p.?	Pathogenic
M7	BRCA2	deletion-insertion	c.7762_7764delinsTT	p.Ile2588Phefs*60	Pathogenic
M8	BRCA1	small deletion	c.2433del	p.Lys812Argfs*3	Pathogenic
M9	ATM	nonsense	c.103C>T	p.Arg35*	Pathogenic
M10	BRCA2	small deletion	c.4936_4939del	p.Glu1646Glnfs*23	Pathogenic
M11	MSH2	duplication	c.2005+2dupT	p.?	Pathogenic
M12	BRCA2	small deletion	c.5164_5167del	p.Ser1722Leufs*2	Pathogenic
M13	MLH1	missense/splicing	c.793C>T	p.His264Leufs*2	Pathogenic
M14	BRCA2	small deletion	c.6174del	p.Phe2058Leufs*12	Pathogenic
M15	APC	nonsense	c.1903G>T	p.Gly635*	Pathogenic
M16	TP53	deletion	deletion exon 2-11	p.?	Pathogenic
M17	BRCA1	splicing mutation	c.134+5G>A	p.?	Pathogenic
M18	BRCA2	small deletion	c.6174del	p.Phe2058Leufs*12	Pathogenic
M19	P53	nonsense	c.184G>T	p.Glu62*	Pathogenic
M20	MSH2	nonsense	c.2131C>T	p.Arg711*	Pathogenic
M21	BRCA2	nonsense	c.5645C>A	p.Ser1882*	Pathogenic
M22	BRCA2	small deletion	c.3398_3402del	p.Pro1133Leufs*9	Pathogenic
M23	BRCA2	small deletion	c.5582_5583del	p.Lys1861Serfs*11	Pathogenic
M24	BRCA2	nonsense	c.5857G>T	p.Glu1953*	Pathogenic
M25	BRCA2	nonsense	c.9182T>G	p.Leu3061*	Pathogenic
M26	BRCA2	nonsense	C.9294C>G	p.Tyr3098*	Pathogenic
M27	BRCA2	small deletion	c.755_758del	p.Asp252Valfs*24	Pathogenic
M28	BRCA1	deletion	Exons 8-11	p.?	Pathogenic
M29	BRCA2	small deletion	c.3847_3848del	p.Val1283Lysfs*2	Pathogenic

Supplementary Table 4. NCCN guidelines for pancreatic cancer testing

NCCN guidelines criteria for pancreatic cancer testing
• Personal history of pancreatic cancer at any age with ≥*1* close blood relative with breast *(≤50 y)* and/or invasive ovarian and/or pancreatic cancer at any age. • Personal history of prostate cancer (Gleason score ≥7) at any age with ≥*1* close blood relative with breast *(≤50 y)* and/or invasive ovarian and/or pancreatic or prostate cancer (Gleason score ≥7) at any age. • *Personal history of* pancreatic cancer, *and* Ashkenazi Jewish ancestry only one additional affected relative is needed.

Supplementary Table 5. Analysis of patients who met NCCN guidelines for pancreatic cancer testing in the HRC.

Met NCCN 2018 Criteria	Yes (n (%))	No (n (%))
HRC all tested (n=277)	141 (50.1)	136 (49.9)
HRC <60 (n= 130)	58 (44.6)	72 (55.4)
HRC Mutation Positive (n=48)	25 (52.1)	23 (47.9)
HRC <60 Mutation Positive (n=29)	12 (41.4)	17 (58.6)

Supplementary Table 6. Patient demographics, personal and family History (n=132) in tested patients from General Cohort, FDR, first-degree relative; SDR, second-degree relative; yrs, years; SD, standard deviation.

Characteristic	**N (%)**
Age	
Mean (yrs (SD))	59.73 (+/-10.15)
Sex	
Female	54 (40.9)
Male	78 (59.1)
Race	
White	111 (84)
Hispanic	6 (4.5)
Black	12 (9)
Asian	3 (2.2)
Stage	
Metastatic	132 (100)
Personal History of Cancer	
Breast	1 (0.8)
Gynecologic	0
Melanoma	0
Colon	0
Family History of Cancer	
≥1 affected FDR	
Pancreas	11 (8.3)
≥1 affected SDR	
Pancreas	9 (6.8)

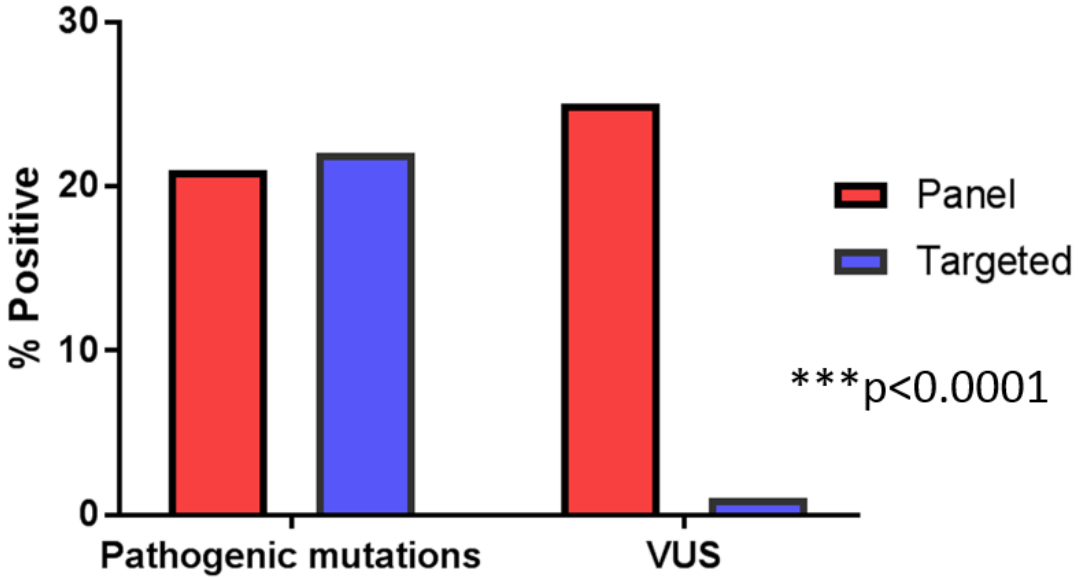
Supplementary Table 7. Comparison of demographic data, clinical characteristics, and family history of cancer in the General Cohort patients between patients that tested positive vs. negative for mutations. VUS were tabulated as negative results. FDR, first-degree relative; SDR, second-degree relative.

Characteristic	**Mutation positive (n=9) n (%)**	**Mutation negative (n=123) n (%)**	**p-value**
Age			
Mean (yrs (SD))	48.44 (+/-9.65)	60.56 (+/-10.57)	**0.033***
Sex			
Female	5 (55.6)	49 (39.8)	0.4857
Male	4 (44.4)	74 (60.2)	
Race			
White	7 (77.7)	104 (84.5)	0.1671
Hispanic	1 (11.1)	5 (4)	
Black	0 (0)	12 (9.75)	
Asian	1 (11.1)	2 (1.62)	
Family History of Cancer			
≥1 affected FDR			
Pancreas	2 (22.2)	9 (7.3)	0.16
≥1 affected SDR			
Pancreas	0 (0)	9 (7.3)	1

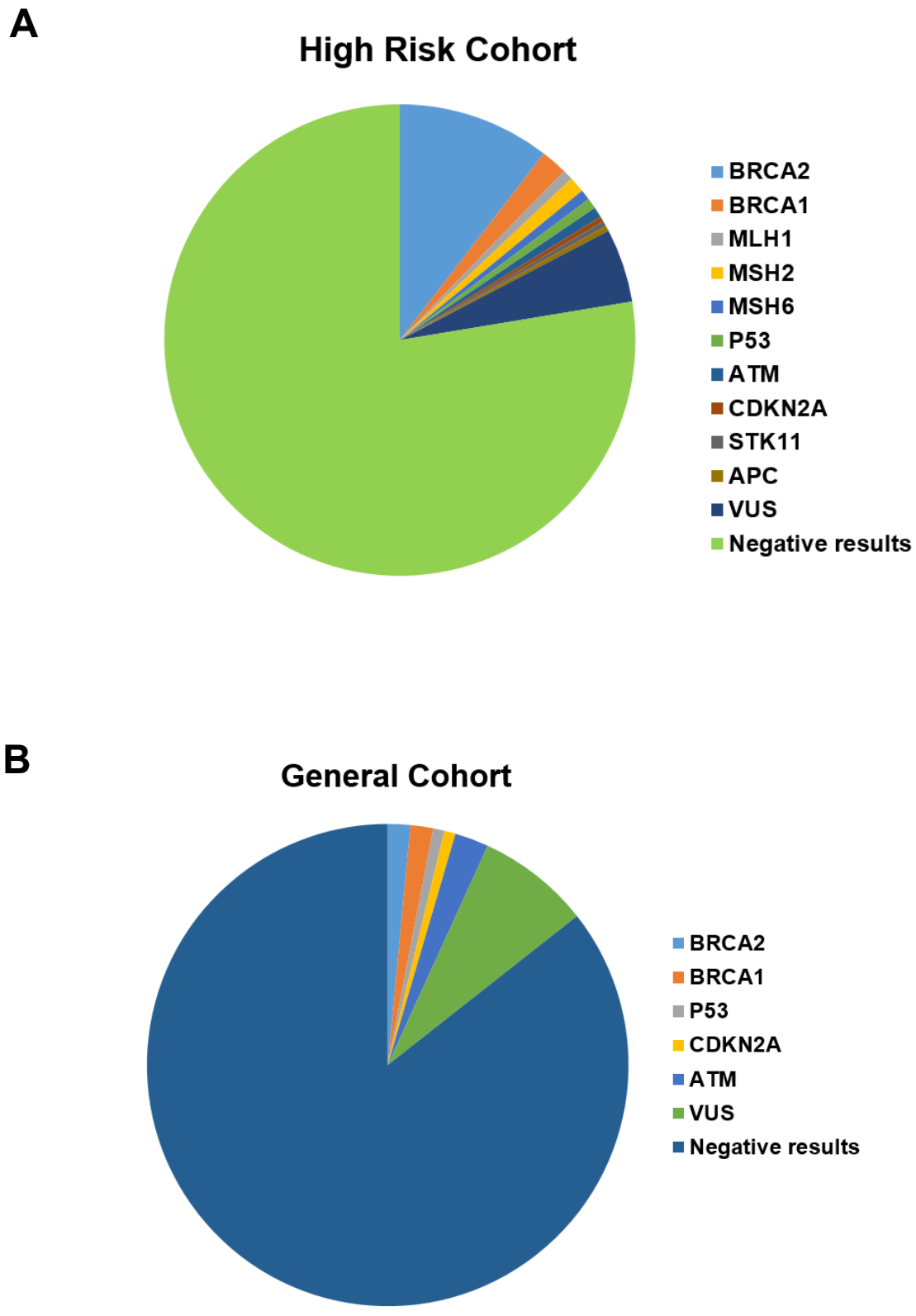
Supplementary Table 8. Comparison of Demographical Information, Clinical Characteristics, and Family History of Cancer in the young onset HRC by Panel or by Single gene testing.

Characteristic	Panel (n=28)	Single gene (n=102)	p-value
Mean age at diagnosis, Years (+/- SD)	50.68 (± 1.55)	51.33 (± 0.6991)	0.675
Sex			
Female	15 (53.5)	44 (43.1)	0.803
Male	13 (46.4)	58 (56.8)	
Race			
White	20 (71.4)	83 (81.3)	0.554
Hispanic	5 (17.8	10 (9.8)	
Black	1 (3.5)	5 (4.9)	
Asian	2 (7.1)	4 (3.9)	

Supplementary Fig 1. Figure depicting percent of tested patients by panel vs. targeted testing with positive pathogenic mutations or VUS results in the young onset HRC. ***p value<0.0001 calculated by Fisher's exact test



Supplementary Fig 2. Mutated genes in High Risk (A) and General (B) Cohorts.



Supplementary Fig 3. Kaplan-Meier Survival curves for metastatic patients in the HRC based on their mutational status (A) and for all metastatic PDAC patients from HRC vs. those without mutations from GC. N= Number of patients in each subgroup.