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## The Multicenter Cancer of Pancreas Screening Study: Impact on Stage and Survival

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# Background

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- Pancreas surveillance has been recommended for individuals estimated to be at high risk of developing PDAC (5% or higher estimated lifetime risk).
- The risk increases with the number of affected first-degree relatives with a pancreatic cancer and in those who carry a pathogenic germline variant.

**Primary outcome:** early detection of stage I PDAC or a noninvasive neoplasm with HGD in CAPS5 (since 2014).

**Secondary outcome:** overall survival after a diagnosis of PDAC or HGD for HRIs enrolled in all CAPS studies (CAPS1-5: 1998-2021), estimated using the Kaplan-Meier method.

# Methods

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- CAPS5: Multicenter, prospective cohort study involving 8 academic centres in US
- **Eligible patients for surveillance:**



Germline susceptibility gene variant with a family history of pancreatic cancer (or without family history if germline alterations in CDKN2A or STK11);

Meeting family history criteria (one first-degree and one second-degree relative with PDAC, or more than one first-degree relative with PDAC);

**Other:** BRCA2 or ATM mutation carriers without a family history, or those with other family history criteria (eg, having 3 SDR with PC, without an affected FDR).

# Methods

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- **Meeting age criteria:**

50-55y

based on family history criteria

45-50y

with a susceptibility gene mutation, (or 10 years younger than the youngest relative with pancreatic cancer)

40y

for carriers of a deleterious *CDKN2A* variant

30-40y

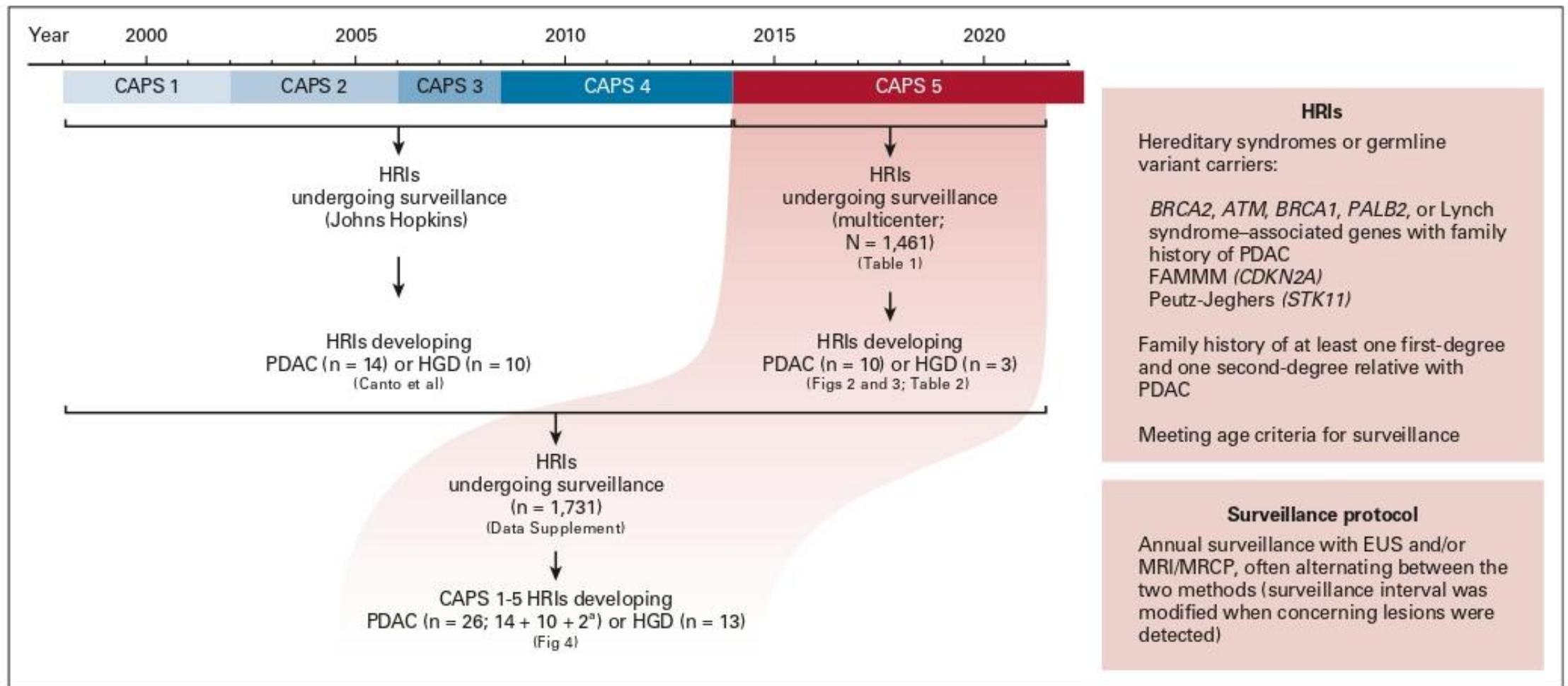
Peutz-Jeghers syndrome

# Methods

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- **Surveillance protocol:**

- Baseline pancreas imaging with endoscopic ultrasound (EUS) **and** magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP);
- Annual surveillance with **alternating** EUS and MRI/MRCP with contrast;
- Pancreatic-protocol computerized tomography (CT) scan was also utilized for surveillance in a few patients (e.g., for claustrophobia, patient preference);
- Pancreatic cancers were considered within surveillance if they underwent surveillance within three months of their recommended surveillance interval.



**FIG 1.** Diagram of the CAPS1-5 enrollment periods from 1998 to 2021 summarizing the outcomes of individuals in the CAPS5 study and combined updated outcomes of the CAPS1-5 studies. A summary of the CAPS5 study criteria and surveillance protocol is provided in the boxes and described with more details in the methods section. <sup>a</sup>Two HRIs from the CAPS1-4 cohort stopped surveillance and then developed PDAC after the last report of that cohort in the study by Canto et al.<sup>14</sup> CAPS, Cancer of Pancreas Screening; EUS, endoscopic ultrasound; FAMMM, familial atypical multiple mole melanoma; HGD, high-grade dysplasia; HRI, high-risk individual; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PDAC, pancreatic ductal adenocarcinoma.

# Results CAPS5

**TABLE 1.** Baseline Characteristics of the Cancer of Pancreas Screening-5 Study Cohort

**High-Risk Cohort** **N = 1,461**

Age, mean $\pm$ SD, years	60.3 $\pm$ 9.7
Sex (female), No. (%)	944 (64.6)
Race/ethnicity, No. (%)	
White	1,380 (94.5)
African American	51 (3.5)
Asian	19 (1.3)
Hispanic/Latino	35 (2.4)
Other/multiple	13 (0.7)

Pathogenic germline variant carriers,  
No. (%)

<i>BRCA2</i> + $\geq$ 1 FDR/SDR with PDAC	269 (18.4)
<i>BRCA1</i> + $\geq$ 1 FDR with PDAC	68 (4.7)
<i>CDKN2A</i> (FAMMM syndrome)	69 (4.7)
Lynch syndrome + $\geq$ 1 FDR/SDR with PDAC	58 (4.0)
<i>PALB2</i> + $\geq$ 1 FDR/SDR with PDAC	62 (4.2)
<i>ATM</i> + $\geq$ 1 FDR/SDR with PDAC	93 (6.4)
Peutz-Jeghers syndrome ( <i>STK11</i> )	18 (1.2)
More than one mutation + $\geq$ 1 FDR/SDR with PDAC	6 (0.4)

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# Results CAPS5

Familial pancreatic cancer without known pathogenic germline variants, No. (%)	
≥ 2 FDR <sup>a</sup>	346 (23.7)
1 FDR + ≥ 1 SDR <sup>b</sup>	402 (27.5)
1 FDR with young onset PDAC ≤ 50 years old	5 (0.3)
Other high-risk cohort (Data Supplement), No. (%)	65 (4.5)
Personal history of cancer, <sup>c</sup> No. (%)	455 (31.1)
Smoking, No. (%)	
Never/former	910/1,420 (64.1)/454 (32.0)
Current	56 (3.9)
Alcohol use (current), No. (%)	733/1,414 (51.8)
Diabetes mellitus (type 1/2), No. (%)	137/1,391 (9.8)

Abbreviations: FAMMM, familial atypical multiple mole melanoma; FDR, first-degree relative; PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation; SDR, second-degree relative.

<sup>a</sup>Excluding two parents with PDAC.

<sup>b</sup>SDR is first-degree relative of FDR with PDAC.

<sup>c</sup>Excluding basal cell or squamous cell skin carcinoma.

# Results CAPS5

**Supplementary Table 1:** Additional risk subgroups within the CAPS5 cohort

Other risk groups within the CAPS5 cohort	Total: 65/1461
• <i>BRCA2</i> without FDR/SDR	24 (1.6%)
• $\geq 2$ SDR	11 (0.8%)
• <i>BRCA1</i> with SDR	10 (0.7%)
• Lynch Syndrome without FDR/SDR	8 (0.5%)
• <i>ATM</i> without FDR/SDR	5 (0.3%)
• <i>BRCA2</i> and <i>ATM</i> without FDR/SDR	2 (0.14%)
• <i>BRCA1</i> without FDR/SDR	2 (0.14%)
• <i>PALB2</i> without FDR/SDR	2 (0.14%)
• 1 SDR 5TDR	1 (0.07%)

FDR: First degree relative, SDR: Second degree relative, TDR: Third degree relative

\*1 additional patient with 1 FDR and 3 TDR is part of the combined CAPS1-5 cohort

Familial pancreatic cancer without known pathogenic germline variants, No. (%)	
$\geq 2$ FDR <sup>a</sup>	346 (23.7)
1 FDR + $\geq 1$ SDR <sup>b</sup>	402 (27.5)
1 FDR with young onset PDAC $\leq 50$ years old	5 (0.3)
Other high-risk cohort (Data Supplement), No. (%)	65 (4.5)
Personal history of cancer, <sup>c</sup> No. (%)	455 (31.1)
Smoking, No. (%)	
Never/former	910/1,420 (64.1)/454 (32.0)
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<sup>b</sup>SDR is first-degree relative of FDR with PDAC.

<sup>c</sup>Excluding basal cell or squamous cell skin carcinoma.

Total 1461 HRIs

451 (30.9%) undergone **one** baseline screening examination

1010 (69.1%)

251 baseline visit  
< 1 year of data extraction

236 baseline visit  
≥ 1 year of data extraction (**not yet** any subsequente visit)

median **FUP 4years**

**TABLE 2.** Screen-Detected PDAC or High-Grade Neoplasms in Cancer of Pancreas Screening-5 Study

Case	Age (years)	Risk Group	Baseline/Surveillance	Lesion Detected on Diagnostic Imaging	Tumor Location, Type of Surgery	Pathology (eighth AJCC)	Stage if Cancer (eighth AJCC)	Survival (dead/alive, years since PDAC/HGD diagnosis)
1	74	Familial 1 FDR + $\geq 1$ SDR	Surveillance (prior MRI 14 months previously)	New main pancreatic duct dilation (to 7 mm), no mass seen—1.5-cm mass by pathology (also an unrelated 1.3-cm pancreatic cyst)	BOP, Whipple	PDAC pT1NOMO	IA	Alive, 2.2
2	59	BRCA2 with FDR/SDR	Surveillance (prior EUS 11 months previously)	1-cm mass	HOP, Whipple	PDAC pT1NOMO	IA	Alive, 0.4
3	56	CDKN2A (FAMMM)	Surveillance (prior EUS 12 months previously)	1.1-cm mass	TOP, distal pancreatectomy	PDAC pT1NOMO	IA	Alive, 1.9
4	58	Familial 1 FDR + $\geq 1$ SDR	Baseline	1.7-cm mass	BOP, distal pancreatectomy	PDAC pT2NOMO	IB	Alive, 4.1
5	57	Familial $\geq 2$ FDR	Baseline	1.6-cm mass	TOP, distal pancreatectomy	PDAC pT1NOMO	IB	Alive, 2.6
6	63	PALB2 with FDR/SDR	Baseline	1.6-cm mass	HOP, Whipple	PDAC ypT1NOMO	IA by surgical pathology (and at detection by imaging)	Alive, 0.8
7	59	Familial 1 FDR + $\geq 1$ SDR	Baseline	5-cm mass	TOP, distal pancreatectomy	PDAC ypT2NOMO	IB by surgical pathology, (2A at detection by imaging)	Dead, 3.8
8	69	Familial $\geq 2$ FDR	Surveillance (prior MRI 6 months earlier)	2.1-cm mass	HOP, Whipple	PDAC pT2N1M0	IIB	Alive, 3.5
9	65	BRCA1 with SDR	Surveillance (prior EUS 6 months previously)	2.5-cm SMA involvement	HOP	PDAC T4M0 (clinical stage; did not have surgery)	III	Dead, 1.4
10	74	BRCA2 with FDR/SDR	Outside surveillance, 4 years, symptomatic	2.6-cm mass	TOP	PDAC, M1 (peritoneal spread)	IV	Alive, 2
11	77	BRCA2 with FDR/SDR	Surveillance	Rapidly enlarging cyst > 2 cm, no worrisome features	BOP, distal pancreatectomy	IPMN with LGD, high-grade PanIN	NA	Alive, 2.8
12	72	Familial 1 FDR + $\geq 1$ SDR	Surveillance	2.6-cm cyst without worrisome features	TOP, distal pancreatectomy	IPMN HGD	NA	Alive, 0.5
13	63	BRCA1 with FDR	Surveillance	Septated 1-cm cyst with HGD on FNA	BOP, distal pancreatectomy	IPMN HGD, high-grade PanIN	NA	Alive, 3.1

During the CAPS5 surveillance period:

- 9 PDAC

Stage	n
I	7
IIB	1
III	1

8/9 resectable

4/9 baseline detected

- 1 metastatic PDAC, symptomatic, outside surveillance 4 years after baseline screening

Abbreviations: AJCC, American Joint Committee on Cancer; BOP, body of pancreas; EUS, endoscopic ultrasound; FAMMM, familial atypical multiple mole melanoma; FDR, first-degree relative; FNA, fine-needle aspiration; HGD, high-grade dysplasia; HOP, head of pancreas; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; MRI, magnetic resonance imaging; NA, not available; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; SDR, second-degree relative; SMA, superior mesenteric artery; TOP, tail of pancreas.

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2	59	<i>BRCA2</i> with FDR/SDR	Surveillance (prior EUS 11 months previously)	1-cm mass	HOP, Whipple	PDAC pT1NOMO	IA	Alive, 0.4
3	56	<i>CDKN2A</i> (FAMMM)	Surveillance (prior EUS 12 months previously)	1.1-cm mass	TOP, distal pancreatectomy	PDAC pT1NOMO	IA	Alive, 1.9
4	58	Familial 1 FDR + $\geq 1$ SDR	Baseline	1.7-cm mass	BOP, distal pancreatectomy	PDAC pT2NOMO	IB	Alive, 4.1
5	57	Familial $\geq 2$ FDR	Baseline	1.6-cm mass	TOP, distal pancreatectomy	PDAC pT1NOMO	IB	Alive, 2.6
6	63	<i>PALB2</i> with FDR/SDR	Baseline	1.6-cm mass	HOP, Whipple	PDAC ypT1NOMO	IA by surgical pathology (and at detection by imaging)	Alive, 0.8
7	59	Familial 1 FDR + $\geq 1$ SDR	Baseline	5-cm mass	TOP, distal pancreatectomy	PDAC ypT2NOMO	IB by surgical pathology, (2A at detection by imaging)	Dead, 3.8
8	69	Familial $\geq 2$ FDR	Surveillance (prior MRI 6 months earlier)	2.1-cm mass	HOP, Whipple	PDAC pT2N1M0	IIB	Alive, 3.5
9	65	<i>BRCA1</i> with SDR	Surveillance (prior EUS 6 months previously)	2.5-cm SMA involvement	HOP	PDAC T4M0 (clinical stage; did not have surgery)	III	Dead, 1.4
10	74	<i>BRCA2</i> with FDR/SDR	Outside surveillance, 4 years, symptomatic	2.6-cm mass	TOP	PDAC, M1 (peritoneal spread)	IV	Alive, 2
11	77	<i>BRCA2</i> with FDR/SDR	Surveillance	Rapidly enlarging cyst > 2 cm, no worrisome features	BOP, distal pancreatectomy	IPMN with LGD, high-grade PanIN	NA	Alive, 2.8
12	72	Familial 1 FDR + $\geq 1$ SDR	Surveillance	2.6-cm cyst without worrisome features	TOP, distal pancreatectomy	IPMN HGD	NA	Alive, 0.5
13	63	<i>BRCA1</i> with FDR	Surveillance	Septated 1-cm cyst with HGD on FNA	BOP, distal pancreatectomy	IPMN HGD, high-grade PanIN	NA	Alive, 3.1

During the CAPS5 surveillance period:

- 8 pancreatic resections for cystic lesions detected during surveillance

**3/8 HGD/Displasia**

Abbreviations: AJCC, American Joint Committee on Cancer; BOP, body of pancreas; EUS, endoscopic ultrasound; FAMMM, familial atypical multiple mole melanoma; FDR, first-degree relative; FNA, fine-needle aspiration; HGD, high-grade dysplasia; HOP, head of pancreas; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; MRI, magnetic resonance imaging; NA, not available; PanIN, pancreatic intraepithelial neoplasia; PDAC, pancreatic ductal adenocarcinoma; SDR, second-degree relative; SMA, superior mesenteric artery; TOP, tail of pancreas.

# Results CAPS5

- Other cancers detected during surveillance

Supplementary Table 3: Other incident cancers in the CAPS5 study

	Frequency	Percent
AML	2	2.7
Appendix	1	1.3
bladder	3	4
Breast	17	22.7
Cervical	1	1.3
CLL	2	2.7
Colorectal	6	8
Glioblastoma	1	1.3
Lung	5	6.7
Lymphoma	3	4
Melanoma	7	9.3
Ovarian	2	2.7
Prostate	11	14.7
Renal	6	8
Sarcoma	3	4
Squamous cell of Vocal Cord	1	1.3
Thyroid	1	1.3
Unknown primary	1	1.3
Total	73	100

# Results CAPS1-5

- Median FUP 2.8 years

**Supplementary Table 4:** Baseline characteristics of the combined CAPS1-5 cohort

Standard deviation (SD); first degree relative (FDR); second degree relative (SDR); pancreatic ductal adenocarcinoma (PDAC); familial atypical multiple mole melanoma (FAMMM)

	Total: 1731
Age, mean + SD	59.2 ±10
Gender (Females)	1095 (63.3%)
Race/Ethnicity	
• White	1638 (94.6%)
• Black or African American	56 (3.2%)
• Asian	21 (1.2%)
• Other/multiple	16 (0.9%)
• Hispanic/Latino	41(2.9%)
High-Risk cohort:	
-Pathogenic Germline Mutation Carriers/Hereditary cancer syndromes	
• <i>BRCA2</i> + ≥1 FDR/SDR with PDAC	285 (16.5%)
• <i>BRCA1</i> + ≥1 FDR with PDAC	76 (4.4%)
• <i>CDKN2A</i> (FAMMM syndrome)	73 (4.2%)
• Peutz-Jeghers syndrome ( <i>STK11</i> )	26 (1.5%)
• Lynch Syndrome + ≥1 FDR/SDR with PDAC	58 (3.4%)
• <i>PALB2</i> + ≥1 FDR/SDR with PDAC	64 (3.7%)
• <i>ATM</i> + ≥1 FDR/SDR with PDAC	96 (5.5%)
• More than one mutation + ≥1 FDR/SDR with PDAC	6 (3.5%)
-Familial Pancreatic cancer without known pathogenic germline mutations	
• ≥ 2 FDR*	446 (25.8%)
• 1 FDR + ≥1 SDR**	527 (30.4%)
• 1 FDR with young onset PDAC ≤50 years old	8 (0.5%)
-Other high-risk cohort (Supplementary Table 1)	66 (3.8%)

\*Excluding two parents with PDAC

\*\* SDR is first-degree relative of FDR with PDAC

# Results CAPS1-5

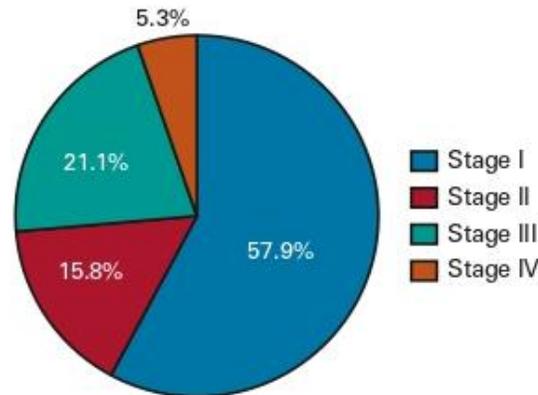
26 patients had a diagnosis of PDAC

- 19 detected during surveillance (A)

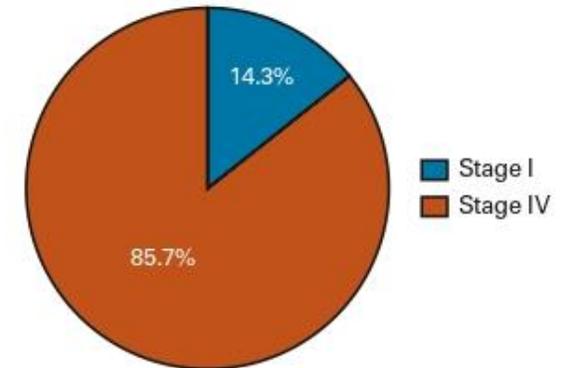
vs 7 outside surveillance (B) (6/7 stage IV)

Stage	N (%)
I	15 (57.9)
II	4 (15.8)
III	6 (21.1)
IV	1 (5.2)

A



B



10/26 (38,5%) had a known pathogenic germline variant

# Results CAPS1-5

26 patients had a diagnosis of PDAC

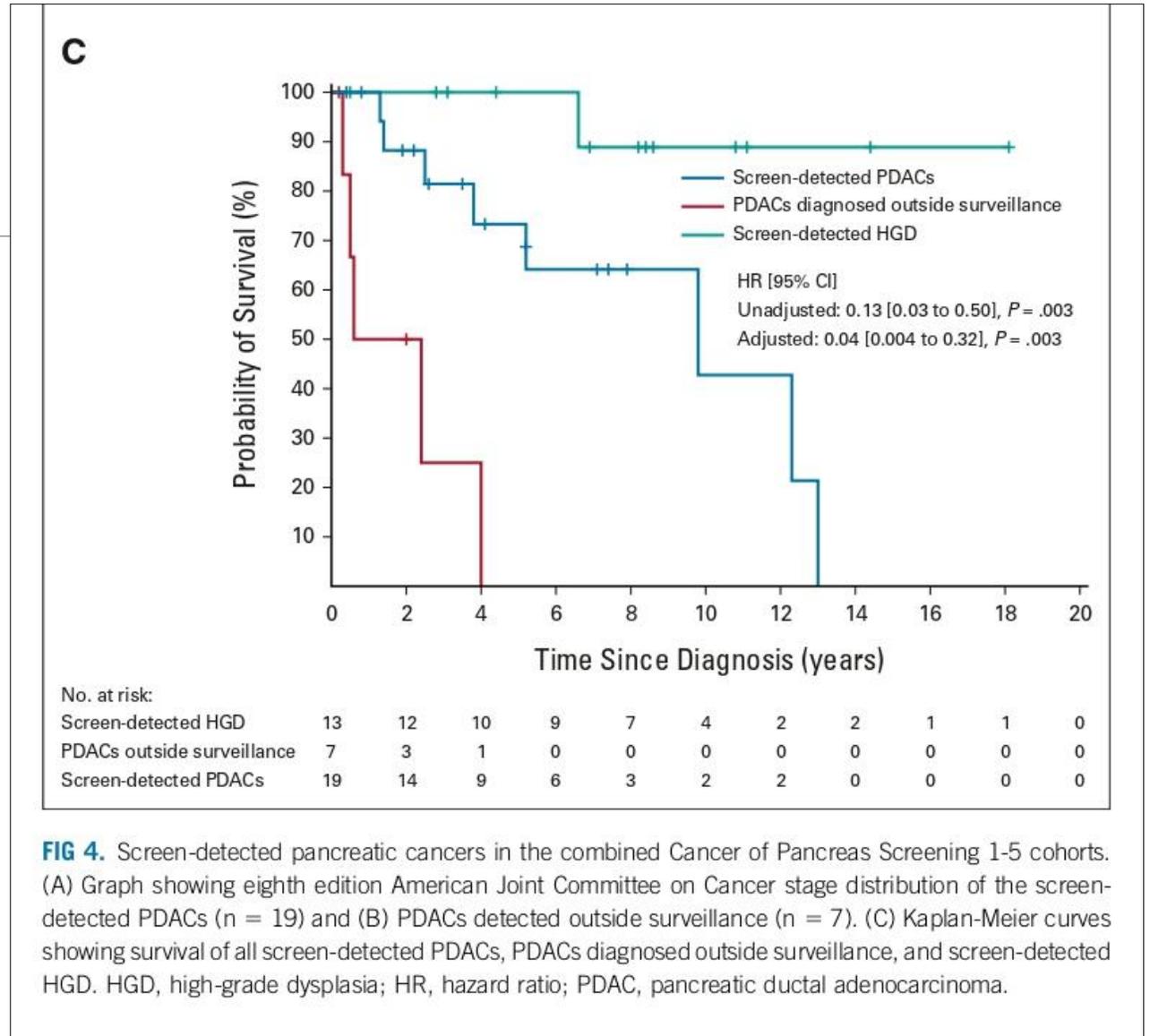
Median survival:

Screen-detected PDAC 9.8years

(5 year survival 73.3%)

VS

PDAC outside surveillance 1.5years



# Discussion

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- Among HRIs undergoing surveillance in the CAPS5 study, PDAC was diagnosed in one of every 160 person-years (predominance of stage I PDACs), and a median survival of 9.8 years.
- The survival benefit associated with pancreas surveillance is clearly evident in the entire CAPS cohort (CAPS1-5) with long-term follow-up; the 5-year overall survival among screen-detected PDACs was 73.3% in this updated analysis.
- Further evidence of the value of regular surveillance and appropriate surgical intervention of IPMN with HGD without an IPMN-associated invasive ductal adenocarcinoma.
- Longer follow-up is needed to better define the benefits of EUS and MRIbased surveillance in high-risk cohorts, along with long-term studies designed to evaluate the role of emerging biomarker tests.