**PURPOSE** To report pancreas surveillance outcomes of high-risk individuals within the multicenter Cancer of Pancreas Screening-5 (CAPS5) study and to update outcomes of patients enrolled in prior CAPS studies.

**METHODS** Individuals recommended for pancreas surveillance were prospectively enrolled into one of eight CAPS5 study centers between 2014 and 2021. The primary end point was the stage distribution of pancreatic ductal adenocarcinoma (PDAC) detected (stage I vs higher-stage). Overall survival was determined using the Kaplan-Meier method.

**RESULTS** Of 1,461 high-risk individuals enrolled into CAPS5, 48.5% had a pathogenic variant in a PDAC-susceptibility gene. Ten patients were diagnosed with PDAC, one of whom was diagnosed with metastatic PDAC 4 years after dropping out of surveillance. Of the remaining nine, seven (77.8%) had a stage I PDAC (by surgical pathology) detected during surveillance; one had stage II, and one had stage III disease. Seven of these nine patients with PDAC were alive after a median follow-up of 2.6 years. Eight additional patients underwent surgical resection for worrisome lesions; three had high-grade and five had low-grade dysplasia in their resected specimens. In the entire CAPS cohort (CAPS1-5 studies, 1,731 patients), 26 PDAC cases have been diagnosed, 19 within surveillance, 57.9% of whom had stage I and 5.2% had stage IV disease. By contrast, six of the seven PDACs (85.7%) detected outside surveillance were stage IV. Five-year survival to date of the patients with a screen-detected PDAC is 73.3%, and median overall survival is 9.8 years, compared with 1.5 years for patients diagnosed with PDAC outside surveillance (hazard ratio [95% CI]; 0.13 [0.03 to 0.50], P = .003).

**CONCLUSION** Most pancreatic cancers diagnosed within the CAPS high-risk cohort in the recent years have had stage I disease with long-term survival.

J Clin Oncol 40:3257-3266. © 2022 by American Society of Clinical Oncology

**INTRODUCTION** Pancreatic cancer is a deadly disease that is projected to become the second most common cause of cancer death in the United States by 2026, with a similar trend of increasing worldwide incidence. Pancreatic cancer survival has improved modestly in recent years; overall 5-year survival now approaches 11%, the poor survival largely attributed to the late stage at diagnosis for most patients. In particular, very few patients are diagnosed with stage I pancreatic ductal adenocarcinoma (PDAC). However, the percentage of patients diagnosed with stage I PDAC has been increasing in the United States in the past decade, which may be due to a number of factors, including improvements in diagnostic imaging, better access to care leading to earlier diagnosis of symptomatic disease (a stage I PDAC diagnosis associated with having better insurance coverage), and the enrollment of more at-risk individuals (with familial/genetic risk and/or incidentally detected pancreatic cysts) into pancreatic surveillance programs.

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 pancreatic cancer and in those who carry a pathogenic germline variant in a pancreatic cancer susceptibility gene. The goals of pancreas surveillance are to reduce pancreatic cancer mortality through early detection, at a stage when the disease is most curable (stage I PDAC), or when there is only a noninvasive neoplasm with high-grade dysplasia (HGD), and to do so with minimal harm. In 2019, the US Preventative Services Task Force recommended against pancreas screening of asymptomatic average-risk adults and those with a family history, but it did not address the role of surveillance in germline mutation carriers. Recent evidence indicates that pancreas
surveillance can downstage pancreatic cancers diagnosed in high-risk individuals (HRIs), although this is based upon only a few studies,12,14-16 with relatively few PDACs diagnosed, and only a small percentage of which were diagnosed with stage I disease.17

The goal of this study was to describe the outcomes to date of the multicenter Cancer of Pancreas Screening-5 (CAPS5) study, which opened in 2014, in particular with a focus on the number of stage I PDACs diagnosed, and to provide updated survival outcomes in the 20+ year CAPS (1998-2021) program overall.

METHODS

Study Design and Participants

CAPS5 (ClinicalTrials.gov identifier: NCT02000089) is a multicenter, prospective cohort study involving eight academic medical centers in the United States that opened to enrollment in 2014; we report on all HRIs enrolled until June 2021. CAPS5 was approved by the Johns Hopkins Institutional Review Board and the institutional review boards at each of the CAPS sites with written informed consent provided by all participants. CAPS5 enrolled patients recommended by the study clinicians to undergo pancreatic surveillance because of their estimated elevated risk of developing PDAC (Fig 1) as per the CAPS international consensus guidelines.5,6 A small percentage of patients (described in the Data Supplement [online only]), were enrolled based upon other risk criteria, such as BRCA2 or ATM mutation carriers without a family history,18 or those with other family history criteria (eg, having three second-degree relatives with pancreatic cancer, without an affected first-degree relative). CAPS participants were enrolled on the basis of recommended age criteria.5,6

In this report, we also provide an updated analysis of the Johns Hopkins CAPS study single-center experience since 1998 (this CAPS1-4 study cohort was described previously14), combining it with the multicenter CAPS5 study cohort data (Fig 1). For patients enrolled in earlier CAPS studies, the follow-up time was calculated from the time of initial baseline screening until the date of last follow-up (see also the Data Supplement for additional methods).

Statistics

The primary outcome of this study was the early detection of stage I PDAC (PDACs were staged per the American Joint Committee on Cancer staging manual, eighth edition) or a noninvasive neoplasm with HGD among HRIs undergoing surveillance, which is reported descriptively with frequencies and percentages. Separate analyses are provided for the CAPS5 cohort and for those enrolled in all the CAPS programs (CAPS1-5). The latter analysis includes an update (since 2017) of the outcomes of patients who progressed to PDAC or a noninvasive neoplasm with HGD since the last CAPS report.14 The study’s secondary outcome was overall survival after a diagnosis of PDAC or HGD for HRIs enrolled in all CAPS studies (CAPS1-5), which was estimated using the Kaplan-Meier method. Overall survival of individuals diagnosed with PDAC was compared between those in the CAPS program whose disease was or was not screen-detected (ie, diagnosed during routine surveillance as opposed to presenting with concerning symptoms outside of surveillance or between surveillance intervals) with Cox proportional hazards models. We report hazard ratios (HRs) both unadjusted and adjusted for age at diagnosis and whether patients were enrolled for family history or pathogenic variant in a PDAC susceptibility gene.

RESULTS

Study Population

The baseline characteristics of the 1,461 subjects in the CAPS5 study cohort are presented in Table 1. 48.5% of...
participants had a pathogenic germline variant, including 18.4% with a BRCA2 and 6.4% with an ATM variant. Around one third of the cohort had a personal history of cancer, with breast cancer being the most commonly reported cancer (15.8% of the entire cohort). To date, 451 (30.9%) of the total CAPS5 cohort have undergone one baseline screening examination (due in part to COVID-19–related delays). Of these 451 HRIs, 215 (47.7%) of the participants had their baseline screening visit less than a year from the date of data extraction, whereas the remaining 236 patients or 16.1% of the entire HRI cohort had a baseline screening visit (≥ 1 year from data extraction date) that has not yet been followed up with any subsequent surveillance. The remaining 1010 HRIs (69.1%) had a median follow-up duration of 4 years (interquartile range, 2.2-5.6 years) for a total of 4,462 person-years of surveillance.

Pancreatic Cancers and Other Resected Lesions

During the CAPS5 study surveillance period, nine patients were diagnosed with a screen-detected PDAC (either at baseline or at subsequent surveillance visits). One additional patient presented with symptomatic metastatic PDAC 4 years after their baseline and only surveillance (Table 2). The majority of pancreatic cancers detected during surveillance (7/9, 77.8%) were stage I by surgical pathology (n = 4 stage IA, n = 3 stage IB); one patient had stage IIB cancer (case 8), and one (case 9) had a stage III cancer (clinically staged) with superior mesenteric artery involvement (Fig 2A; case 9 did not undergo surgical resection). Overall, 8/9 (88.9%) of the screen-detected PDACs were resectable. Two of the stage I PDACs were surgically staged after neoadjuvant chemotherapy (their stages at diagnosis by imaging, before neoadjuvant therapy were stage IA and IIA, Table 2). The PDACs detected during surveillance were detected between 6 and 14 months after their previous imaging test (Table 2). Most of the PDACs were detected by imaging as small pancreatic masses; one case had concerning main pancreatic duct dilation without a detectable mass; none of the PDACs arose from an intraductal papillary mucinous neoplasm (IPMN). Comparing the proportion of stage I PDACs to the national average is highly significant; in 2016, 5.4% of 8,398 PDACs in the SEER database (National Cancer Institute-SEER) were stage I by surgical pathology (P < .00001, Fisher’s exact test).

Seven of the nine patients diagnosed with a screen-detected PDAC are alive, with median overall survival to date of 3.84 years. The Kaplan-Meier survival curves of the patients with PDAC and a noninvasive neoplasm with HGD are shown in Figure 2B. Seven patients are alive at last follow-up; one patient with stage IB PDAC (BRCA1) and another who had stage III PDAC (familial-risk) died after 3.84 and 1.4 years from diagnosis, respectively. One patient (stage IB) had a biopsy-proven lung recurrence 1.7 years after surgery, but is currently alive (4.1 years after surgery). The one patient (BRCA2) diagnosed with PDAC 4 years after dropping out of surveillance, who was also diagnosed with colorectal cancer around the same time, is still alive 2 years after diagnosis.
TABLE 1. Baseline Characteristics of the Cancer of Pancreas Screening-5 Study Cohort

| Pathogenic Germline Variant Carriers, No. (%)                                      | 
|----------------------------------------------------------------------------------|
| BRCA2 + ≥ 1 FDR/SDR with PDAC                                                   | 269 (18.4) |
| BRCA1 + ≥ 1 FDR with PDAC                                                       | 68 (4.7) |
| CDKN2A (FAMMM syndrome)                                                         | 69 (4.7) |
| Lynch syndrome + ≥ 1 FDR/SDR with PDAC                                          | 58 (4.0) |
| PALB2 + ≥ 1 FDR/SDR with PDAC                                                   | 62 (4.2) |
| ATM + ≥ 1 FDR/SDR with PDAC                                                     | 93 (6.4) |
| Peutz-Jeghers syndrome (STK11)                                                  | 18 (1.2) |
| More than one mutation + ≥ 1 FDR/SDR with PDAC                                  | 6 (0.4) |

| Familial Pancreatic Cancer Without Known Pathogenic Germline Variants, No. (%)  |
|--------------------------------------------------------------------------------|
| ≥ 2 FDR                                                                         | 346 (23.7) |
| 1 FDR + ≥ 1 SDR                                                                | 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, No. (%)                                             |
|--------------------------------------------------------------------------------|
| 455 (31.1)                                                                      |

| Smoking, No. (%)                                                                |
|--------------------------------------------------------------------------------|
| 56 (3.9)                                                                        |

| 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. *Excluding two parents with PDAC. **Excluding basal cell or squamous cell skin carcinoma.

In addition, eight patients had pancreatic resections for concerning cystic lesions detected during surveillance; three were found to have HGD (in high-grade pancreatic intraepithelial neoplasia or IPMN; summarized in Table 2). The remaining five patients who underwent surgical resection for worrisome lesions had only low-grade dysplasia (Data Supplement).20 There were no significant surgical complications.

Overall, 10 (56%) of the 18 patients identified with PDAC or who underwent surgical resection had pathologies that meet recommended goals of surveillance (seven stage I PDAC, and three with a precancerous neoplasm with HGD).6 During the CAPS5 study period, 73 patients under pancreas surveillance were diagnosed with other cancers, an incidence of 1.68 cancers per 100 patient-years of follow-up. The most common cancers diagnosed were breast (n = 17), prostate (n = 11), and melanoma (n = 7; Data Supplement).

CAPS1-5 Combined Cohort

The 1,731 HRIs (42.6% with germline mutations) enrolled into the CAPS1-5 studies to date have had a median follow-up of 2.8 years (interquartile range, 1.4-4.8 years) with a total of 5,041 person-years of surveillance (their baseline characteristics are described in the Data Supplement). Overall, 26 patients in the entire CAPS program have had a diagnosis of PDAC over the past 20+ years, corresponding to a detection rate (including baseline and surveillance) of 5.15 PDACs diagnosed per 1,000 person-years of surveillance; one individual diagnosed with PDAC per year for every 194 screened. Since the last CAPS report (which described outcomes of CAPS1-4 subjects up to 201714), two additional HRIs, one who had enrolled into the CAPS4 and one who had enrolled into CAPS3, developed PDAC outside of surveillance (both stage IV), at 4 and 7 years, respectively, after their last pancreas surveillance imaging. Among the 26 patients with PDAC, 38.5% (10/26) had a known pathogenic germline variant (10 of the 16 without a known variant had undergone negative multigene panel testing). Since 2018, National Comprehensive Cancer Network guidelines have recommended individuals with PDAC and their first-degree relatives be offered susceptibility gene testing.21,22 Among the 26 PDACs, 19 were detected during surveillance, 57.9% of whom had stage I disease, 15.8% stage II, 21.1% stage III, and 5.2% stage IV (Fig 4A). In the CAPS1-5 cohort, six of the seven cases (85.7%) whose PDAC was detected outside surveillance were stage IV (Fig 4B). The median (standard deviation/range) age at diagnosis for all PDAC cases was 65.5 (9.5/45-81) years; for those with stage I PDAC, it was 65.3 (7.8/57-77) years; for those with stage IV, it was 69.1 (8.9/59-81) years (P = .37). Regarding management

Figure 3 (case 2) shows an example of a stage IA PDAC detected by using magnetic resonance imaging (MRI) performed 1 year after a normal-appearing endoscopic ultrasound (EUS; Data Supplement). The Data Supplement shows another case of a stage IA PDAC detected by surveillance EUS as a 1.1-cm hypoechoic mass and confirmed with secretin-enhanced MRI/magnetic resonance cholangiopancreatography (case 3).
| 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 + ≥ 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 pT1N0M0 | IA | Alive, 2.2 |
| 2    | 59         | BRCA2 with FDR/SDR | Surveillance (prior EUS 11 months previously) | 1-cm mass | HOP, Whipple | PDAC pT1N0M0 | IA | Alive, 0.4 |
| 3    | 56         | CDKN2A (FAMMM) | Surveillance (prior EUS 12 months previously) | 1.1-cm mass | TOP, distal pancreatectomy | PDAC pT1N0M0 | IA | Alive, 1.9 |
| 4    | 58         | Familial 1 FDR + ≥ 1 SDR | Baseline | 1.7-cm mass | BOP, distal pancreatectomy | PDAC pT2N0M0 | IB | Alive, 4.1 |
| 5    | 57         | Familial ≥ 2 FDR | Baseline | 1.6-cm mass | TOP, distal pancreatectomy | PDAC pT1N0M0 | IB | Alive, 2.6 |
| 6    | 63         | PALB2 with FDR/SDR | Baseline | 1.6-cm mass | HOP, Whipple | PDAC ypT1N0M0 | IA by surgical pathology (and at detection by imaging) | Alive, 0.8 |
| 7    | 59         | Familial 1 FDR + ≥ 1 SDR | Baseline | 5-cm mass | TOP, distal pancreatectomy | PDAC ypT2N0M0 | IB by surgical pathology, (2A at detection by imaging) | Dead, 3.8 |
| 8    | 69         | Familial ≥ 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 + ≥ 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 |

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.
of IPMN, 10 patients had resections of IPMN with HGD, but none of the resected PDACs were associated with an IPMN by surgical pathology. Individuals in the CAPS1-5 cohort with screen-detected PDAC had a significantly longer survival than those whose PDACs were diagnosed outside surveillance (HR unadjusted:

![Image of PDAC stage and survival in the CAPS5 study cohort.](image)

**FIG 2.** PDAC stage and survival in the CAPS5 study cohort. (A) Distribution of stages (eighth edition American Joint Committee on Cancer) of screen-detected PDACs (n = 9) detected during surveillance. (B) Kaplan-Meier curve showing overall survival of all screen-detected PDACs and high-grade neoplasms in the CAPS5 study. CAPS, Cancer of Pancreas Screening; HGD, high-grade dysplasia; PDAC, pancreatic ductal adenocarcinoma.

![Image of Example of a screen-detected stage IA pancreatic cancer (case 2).](image)

**FIG 3.** Example of a screen-detected stage IA pancreatic cancer (case 2). (A) Surveillance magnetic resonance imaging showing a new 1-cm hypoenhancing lesion in the head of the pancreas (arrow pointing to mass). (B) Confirmatory EUS showing a 1.5-cm hypoechoic lesion in the head of the pancreas without invasion of nearby vessels with cytology (not shown) diagnostic of a moderately differentiated adenocarcinoma. (C) Confirmatory computed tomography of the abdomen showing a 1.5-cm pancreatic head mass without upstream dilation or atrophy. (D) Whole-slide scanned image of a resected 1.4-cm lesion showing at 5× (E) a moderately differentiated invasive ductal adenocarcinoma confined to the pancreas. EUS, endoscopic ultrasound.
The median survival for the patients with a screen-detected PDAC was 9.8 years (95% CI, 5.2 to ~ years, ~; small sample size precludes upper survival limit estimate), compared with 1.5 years (0.50 to ~ years) for patients whose PDACs were diagnosed outside surveillance (Fig 4C), and the 5-year survival to date of the CAPS screen-detected PDAC cases is 73.3% (54 to 100).

Adjusting for factors besides stage that could affect survival, specifically, age at PDAC diagnosis and risk group (pathogenic variant carriers v familial risk), yielded a slightly larger effect size (HR 0.04 [95% CI, 0.004 to 0.32], \( P = .003 \)).

Overall, of the 13 patients with HGD in IPMN or pancreatic intraepithelial neoplasias who underwent resection, 12 (92%) were alive at last follow-up; one patient died 6.5 years after pancreatic resection of end-stage renal disease (after a kidney transplant for polycystic kidney disease).

**DISCUSSION**

Among HRIs undergoing surveillance in the CAPS5 study, PDAC was diagnosed in one of every 160 person-years and there was a predominance of stage I PDACs among screen-detected PDAC cases is 73.3% (54 to 100). These results compare favorably with the stage at diagnosis of usual PDAC cases diagnosed outside surveillance (> 50% metastatic disease, < 20% localized and resectable, and < 5% surgically staged as stage I [SEER]), but are consistent
with the long-term survival among PDAC cases in the SEER database with stage I disease by surgical pathology.3

The CAPS5 study results differ in some respects from the recent report of the Dutch Familial Pancreatic Cancer Surveillance Study Group.10 This study reported a PDAC resectability rate of only 60%, which may be a function of the predominance of CDKN2A mutation carriers in their high-risk cohort, which have more aggressive disease than other hereditary syndromes and comprised 70% of their patients with an incident pancreatic cancer.24 As a result of this experience, consideration is being given to having CDKN2A carriers undergo more frequent surveillance (such as biannually). A 2016 study by Vasen et al reported stage I PDACs comprised six of the 15 (40%) PDACs detected during surveillance. Although the follow-up period of the screen-detected PDACs diagnosed in the multicenter CAPS5 study cohort to date is relatively short, there is evidence of improved survival, especially when compared with the 11% 5-year overall survival of patients with PDAC in the United States.4

The survival benefit associated with pancreas surveillance is clearly evident in the entire CAPS cohort (CAPS1-5; Fig 4) with long-term follow-up; the 5-year overall survival among screen-detected PDACs was 73.3% in this updated analysis. The patients who progressed to PDAC in our study included carriers with germline pathogenic variants and those who met familial-risk criteria only. This observation is consistent with previous reports that the PDAC risk in the familial group appears significant enough to warrant surveillance.9,10,14 Our results support current CAPS surveillance recommendations and argue against the notion of limiting pancreatic surveillance to those high-risk individuals with known pathogenic mutations.16,25,26 One guideline that deserves re-evaluation and further study in light of the benefits of pancreas surveillance is the recommendation that a family history of PDAC be required for BRCA2 and ATM mutation carriers.27 This recommendation, part of an effort to enroll only highest-risk individuals, was developed in the early years of pancreas surveillance in an effort to optimize outcomes. Further evidence of the value of regular surveillance and appropriate surgical intervention can be inferred from the proportion of cases of IPMN with HGD without an IPMN-associated invasive ductal adenocarcinoma (n = 10), to the number with an IPMN-associated PDAC (n = 0). This proportion is in marked contrast to what is typically observed in surgical series, where IPMN with HGD is commonly associated with an invasive PDAC.28

There were five pancreatic resections performed during the study period for worrisome-type findings (dilated main pancreatic duct and mass-like lesions), which turned out to harbor low-grade dysplasia only. These cases are discussed at a multidisciplinary conference, and the decision to resect is based on clinical judgment in accordance with expert consensus.6,7 By consensus, these patients would likely have been better off not having surgical resection, but it is notable that these five cases represent a smaller proportion of resections for low-grade lesions than has been reported in prior studies14,15,29,30 and likely results from better selection of patients for surgery. The cases that had resections for low-grade dysplasia highlight the limitations of current EUS and MRI imaging to characterize concerning lesions and the need to improve our diagnostic imaging tools to minimize having progress to advanced-stage PDAC, for example, with artificial intelligence–based methods.31,32 the use of accurate circulating blood-based biomarkers (circulating tumor DNA for multicancer detection,33 genotype-stratified cancer antigen 19-94,35), or other approaches.36-38 A blood test for pancreatic cancer early detection would be attractive, but such a test should approach or complement the diagnostic performance of EUS/MRI for stage I PDAC. And the low incidence of PDAC, even in a high-risk cohort such as CAPS, necessitates using sensitive, high-sensitivity (5 98%) tests, as even modest reductions in diagnostic test specificity yield increasing numbers of false-positive tests, especially when multiple testing occurs over many years.

The improvement in surveillance outcomes reported here compared with previous reports is likely the combined effect of multiple factors, including our case mix (CDKN2A carriers appear to have more aggressive disease), the diagnostic performance of our study team, and the cumulative experience gained from undertaking pancreatic screening studies over more than 20 years. Pancreas surveillance of HRIs and the management of screen-detected pancreatic lesions is best done at expert centers by multidisciplinary teams. At the same time, the low diagnostic yield of PDACs in our cohort highlights the need to develop more refined estimates of pancreatic cancer risk. Few studies have evaluated the cost-effectiveness of pancreas surveillance.39,40 Better estimates of risk would help determine who should undergo surveillance, and at what age surveillance should begin. Commencing surveillance closer to the age range when most PDACs are diagnosed is one potential way diagnostic yield and cost-effectiveness could be improved.

Some limitations to our study include our relatively short follow-up of the CAPS study cohort included in this study; however, we do have long-term follow-up of cases from our earlier CAPS studies. Long-term survival outcomes are needed to minimize confounding from lead-time bias. Comparing outcomes of those diagnosed with a screen-detected PDAC to those whose PDAC was diagnosed after dropping out of surveillance is worthwhile because these groups have similar demographic/ risk characteristics, and for whom data on pancreatic cancer outcomes is limited41,43 but the number of such cases was small. Few PDACs have been diagnosed-to-date in the CAPS program; a larger cohort with longer follow-up would generate better precision estimates for the proportion of stage I PDACs diagnosable with surveillance.

In conclusion, pancreatic surveillance of HRIs can dramatically downstage PDACs diagnosed; most of the patients with PDACs diagnosed in the multicenter CAPS5
study to date had stage I disease. The long-term survival among patients in the CAPS cohort is excellent (currently 73.3% 5-year overall survival). Longer follow-up is needed to better define the benefits of EUS and MRI-based surveillance in high-risk cohorts, along with long-term studies designed to evaluate the role of emerging biomarker tests.

REFERENCES

1. Rahib L, Wehner MR, Matrisian LM, et al: Estimated projection of US cancer incidence and death to 2040. JAMA Netw Open 4:e214708, 2021
2. Huang J, Lok V, Ngai CH, et al: Worldwide burden of, risk factors for, and trends in pancreatic cancer. Gastroenterology 160:744-754, 2021
3. Blackford AL, Canto MI, Klein AP, et al: Recent trends in the incidence and survival of stage 1A pancreatic cancer: A Surveillance, Epidemiology, and End Results analysis. J Natl Cancer Inst 112:1162-1169, 2020
4. Siegel RL, Miller KD, Fuchs HE, et al: Cancer statistics, 2022. CA Cancer J Clin 72:7-33, 2022
5. Canto MI, Harincak F, Hruban RH, et al: International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 62:339-347, 2013

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.00298.
6. Goggins M, Overbeek KA, Brand R, et al: Management of patients with increased risk for familial pancreatic cancer: Updated recommendations from the International Cancer of the Pancreas Screening (CAPS) consortium. Gut 69:7-17, 2020

7. Aslanian HR, Lee JH, Canto M: AGA clinical practice update on pancreas cancer screening in high-risk individuals: Expert review. Gastroenterology 159:358-362, 2020

8. Syngal S, Brand RE, Church JM, et al: AGC clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 110:223-262, 2015; quiz 263

9. Abe T, Blackford AL, Tamura K, et al: Deletionserous germline mutations are a risk factor for neoplastic progression among high-risk individuals undergoing pancreatic surveillance. J Clin Oncol 37:1070-1080, 2019

10. Klein AP, Brune KA, Petersen GM, et al: Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 64:2634-2638, 2004

11. Hu C, Hart SN, Polley EC, et al: Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. JAMA 319: 2401-2409, 2018

12. Henrikson NB, Aiello Bowles EJ, Blasi PR, et al: Screening for pancreatic cancer: Updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 322:445-454, 2019

13. Lucas AL, Kastinos F: Screening for pancreatic cancer. JAMA 322:407-408, 2019

14. Canto M, Almario JA, Schuilk RD, et al: Risk of neoplastic progression in individuals at high risk for pancreatic cancer undergoing long-term surveillance. Gastroenterology 155:740-751.e2, 2018

15. Corral JE, Mareth KE, Riegert-Johnson DL, et al: Diagnostic yield from screening asymptomatic individuals at high risk for pancreatic cancer: A meta-analysis of cohort studies. Clin Gastroenterol Hepatol 17:41-53, 2019

16. Overbeek KA, Levin JM, Koopmann BDM, et al: Long-term yield of pancreatic cancer surveillance in high-risk individuals. Gut 71:1152-1160, 2022

17. Overbeek K, Goggins MG, Dbouk M, et al: Timeline of development of pancreatic cancer and implications for successful early detection in high-risk individuals. Gastroenterology 162:772-785.e4, 2022

18. Katona BW, Long JM, Ahmad NA, et al: EUS-based pancreatic cancer surveillance in BRCA1/BRCA2/PALB2/ATM carriers without a family history of pancreatic cancer. Cancer Prev Res (Phila) 14:1033-1040, 2021

19. Katona B, Mahmud N, Dbouk M, et al: COVID-19 related pancreatic cancer surveillance disruptions amongst high-risk individuals. Pancreatology 21:1048-1051, 2021

20. Brune K, Abe T, Canto M, et al: Multifocal neoplastic precursor lesions associated with lobular atrophy of the pancreas in patients having a strong family history of pancreatic cancer. Am J Surg Pathol 30:1067-1076, 2006

21. Daly MB, Pat T, Berry MP, et al: Genetic familial high-risk assessment: Breast, ovarian, and pancreatic, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 19:77-102, 2021

22. Tempero MA, Malafa MP, Al-Hawary M, et al: Pancreatic adenocarcinoma, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 19:439-457, 2021

23. Khalaf N, El-Serag HB, Abrams HR, et al: Burden of pancreatic cancer: From epidemiology to practice. Clin Gastroenterol Hepatol 19.876-884, 2021

24. Vasen HF, Wasser M, van Mil A, et al: Magnetic resonance imaging surveillance detects early-stage pancreatic cancer in carriers of a p16-Leiden mutation. Gastroenterology 140:850-856, 2011

25. Vasen H, Ibrahim I, Ponce CG, et al: Benefit of surveillance for pancreatic cancer in high-risk individuals: Outcome of long-term prospective follow-up studies from three European expert centers. J Clin Oncol 34:2010-2019, 2016

26. Poter TP: Pancreatic cancer surveillance and its ongoing challenges: Is it time to refine our eligibility criteria? Gut 71:1047-1049, 2021

27. Calderwood AH, Sawhney MS, Thosani NC, et al: American Society for Gastrointestinal Endoscopy guideline on screening for pancreatic cancer in individuals with genetic susceptibility: Methodology and review of evidence. Gastrointest Endosc 95:827-854.e3, 2022

28. Khoury RE, Kabir C, Maker VK, et al: What is the incidence of malignancy in resected intraductal papillary mucinous neoplasms? An analysis of over 100 US institutions in a single year. Ann Surg Oncol 25:1746-1751, 2018

29. Dbouk M, Brewer Gutierrez OI, Lennon AM, et al: Guidelines on management of pancreatic cysts detected in high-risk individuals: Methodology and review of evidence. Clin Gastroenterol Hepatol 17:101-117, 2019

30. Canto MI, Kerdshririchairat T, Yeo CJ, et al: Surgical outcomes after pancreatic resection of screening-detected lesions in individuals at high risk for developing pancreatic cancer. J Gastrointest Surg 15:931-936, 2021

31. Kenner B, Charl ST, Kelsen D, et al: Artificial intelligence and early detection of pancreatic cancer: 2020 summative review. Pancreas 50:251-279, 2021

32. Weisberg EM, Chu LC, Park S, et al: Deep lessons learned: Radiology, oncology, pathology, and computer science experts unite around artificial intelligence to strive for earlier pancreatic cancer diagnosis. Diagn Interv Imaging 101:111-115, 2020

33. Lennon AM, Buchanan AH, Kinde I, et al: Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. Science 369:eabz9601, 2020

34. Abe T, Koi C, Kohi S, et al: Gene variants that affect levels of circulating tumor markers increase identification of patients with pancreatic cancer. Clin Gastroenterol Hepatol 18:1161-1169.e5, 2020

35. Tanaka H, Tamura K, Abe T, et al: Serum carboxypeptidase activity and genotype-stratified CA19-9 to detect early-stage pancreatic cancer. Clin Gastroenterol Hepatol 10.1016/j.cgh.2021.10.008 [epub ahead of print on October 11, 2021]

36. Levin JM, Nesteruk K, Visser DI, et al: Optimization of pancreatic juice collection: A first step toward biomarker discovery and early detection of pancreatic cancer. Am J Gastroenterol 115:2103-2108, 2020

37. Suenaq M, Yu J, Shindo K, et al: Pancreatic juice mutation concentrations can help predict the grade of dysplasia in patients undergoing pancreatic surveillance. Clin Cancer Res 24:2963-2974, 2018

38. Yu J, Sadakari Y, Shindo K, et al: Digital next-generation sequencing identifies low-abundance mutations in pancreatic juice samples collected from the duodenum of patients with pancreatic cancer and intraductal papillary mucinous neoplasms. Gut 66:1677-1687, 2017

39. Kuman S, Saumoy M, On A, et al: Threshold analysis of the cost-effectiveness of endoscopic ultrasound in patients at high risk for pancreatic ductal adenocarcinoma. Pancreas 50:807-814, 2021

40. Corral JE, Das A, Bruno MJ, et al: Cost-effectiveness of pancreatic cancer screening in high-risk individuals: An economic analysis. Pancreas 48:526-536, 2019

41. Montpaz P, O'Connor CA, Chiu JF, et al: Pancreas cancer and BRCA: A critical subset of patients with improving therapeutic outcomes. Cancer 127:4393-4402, 2021

42. Ji J, Forst A, Sundquist J, et al: Survival in familial pancreatic cancer. Pancreatology 8:252-256, 2008

43. Yurgelü MB, Chittenden AB, Morales-Oyarvide V, et al: Germ line cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. Genet Med 21:213-223, 2019
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Bryson W. Katona
Other Relationship: Janssen, Immunovia, Epigenomics, Guardant, Freenome, Universal diagnostics
Uncompensated Relationships: Invitae, Ambry, GeneDx

Randall E. Brand
Consulting or Advisory Role: Immunovia, Freenome (Inst)
Research Funding: Immunovia (Inst), Freenome (Inst)

Amitabh Chak
Stock and Other Ownership Interests: Lucid Diagnostics
Honoraria: CDx Diagnostics
Consulting or Advisory Role: US Endoscopy, Microtek
Research Funding: STERIS
Patents, Royalties, Other Intellectual Property: Methods and compositions for detecting gastrointestinal and other cancers US 8415100 B2. Sanford D. Markowitz, Joseph Willis, Amitabh Chak, Rom Leidner. Pending: 2012272697 (Australia) EP 12802150.8 (Europe) 2,840,324 (Canada) Device for Collecting a Biological Sample: Amitabh Chak, Rebecca Blice, Sanford D. Markowitz, Dean Secrest, Dennis Siedlik, Jeffrey Taggart, Joseph E. Willis. Pending: PCT/US14/070060 Methylated Markers of Esophageal Neoplasia. Amitabh Chak, Omar de la Cruz, Thomas LaFramboise, Sanford D. Markowitz, Helen Moinova, Joseph E. Willis. Pending: 62/099,021 (Inst)

Sapna Syngal
Patents, Royalties, Other Intellectual Property: Dana-Farber Cancer Institute has a registered service mark for the PREMM5 model and holds copyrights for the PREMM questionnaires (Inst); Myriad Genetics (through Dana-Farber Cancer Institute) paid an inventor share of the IP (license issue fee)

James J. Farrell
Honoraria: Immunovia
Consulting or Advisory Role: Cook Medical
Research Funding: Immunovia

Fay Kastrinos
Consulting or Advisory Role: Ambry Genetics/Konica Minolta, Immunovia, Iterative Scopes
Research Funding: Immunovia, Janssen

Elena M. Stoffel
Research Funding: Cancer Prevention Pharmaceuticals (Inst)

Linda S. Lee
Consulting or Advisory Role: Boston Scientific, Fujifilm
Research Funding: Fujifilm

Gregory G. Ginsberg
Consulting or Advisory Role: Olympus Medical Systems
Research Funding: Fractyl
Expert Testimony: Cook Medical

Alison P. Klein
Consulting or Advisory Role: OptumInsight, Merck
Research Funding: OptumLabs

Ihab Kamel
Research Funding: Siemens Healthineers

Ralph H. Hruban
Research Funding: Applied Materials Inc

Patents, Royalties, Other Intellectual Property: Dr Hruban has the potential to receive royalty payments from Thrive Earlier Detection Corp for the TERT in bladder cancers and GNAS inventions in an arrangement reviewed and approved by the Johns Hopkins University

Eun Ji Shin
Consulting or Advisory Role: Boston Scientific

Anne Marie Lennon
Patents, Royalties, Other Intellectual Property: Patent for CancerSEEK

Marcia Irene Canto
Consulting or Advisory Role: Castle Biosciences, Bluestar Genomics
Research Funding: Pentax Medical Corporation (Inst), Endogastric Solutions (Inst)

Patents, Royalties, Other Intellectual Property: Royalties from UpToDate, online

Michael Goggins
Patents, Royalties, Other Intellectual Property: Royalty related to licensing as a codiscoverer of PALB2 as a pancreatic cancer susceptibility gene to Myriad Genetics

No other potential conflicts of interest were reported.