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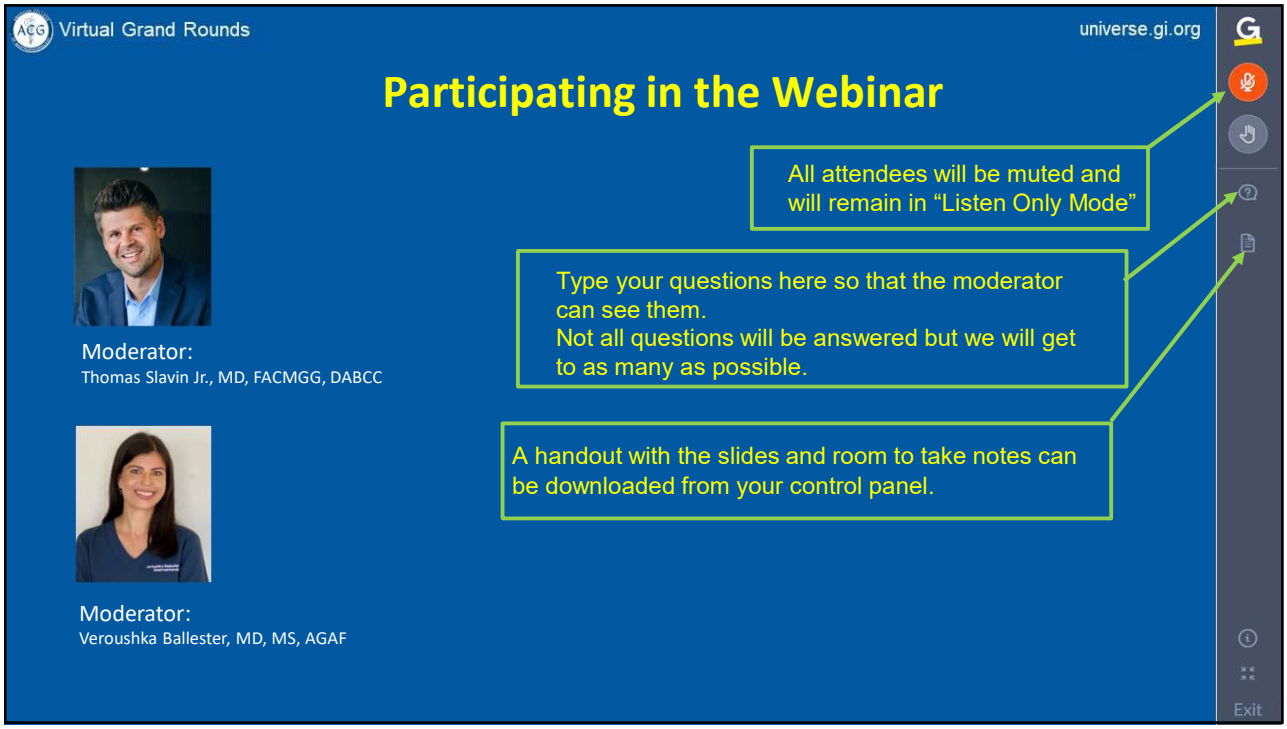
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Not all questions will be answered but we will get to as many as possible.
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Moderator:
Thomas Slavin Jr., MD, FACMGG, DABCC
Moderator:
Veroushka Ballester, MD, MS, AGAF
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Disclosures

Bryson Katona, MD, PhD, AGAF, CGAF:
Clinical trial support (paid to institution): Janssen, Immunovia, Epigenomics, Guardant, Freenome, Universal Diagnostics, Recursion

Beth Dudley Yurkovich, MS, MPH, CGC, CGAF:
No financial relationships

Thomas Slavin Jr., MD, FACMGG, DABCC:
Consultant and shareholder: Myriad genetics
Myriad is public NASDAQ: MYGN

Veroushka Ballester, MD, MS, AGAF:
No financial relationships

**All of the relevant financial relationships listed for these individuals have been mitigated*

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Identification and Management of Hereditary Pancreatic Cancer Risk

Joint ACG/CGA-IGC Webinar

September 28th 2023

Beth Dudley Yurkovich, MS, MPH, CGAF
Certified Genetic Counselor
Division of Gastroenterology, Hepatology, and Nutrition
University of Pittsburgh

Bryson W. Katona, MD, PhD, CGAF
Director, Gastrointestinal Cancer Genetics Program
Assistant Professor of Medicine
Division of Gastroenterology and Hepatology
University of Pennsylvania

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Identification and Management of Hereditary Pancreatic Cancer Risk

- Genetic testing for pancreatic cancer risk syndromes
- Pancreatic cancer risk syndromes
- Who should undergo pancreatic cancer surveillance
- How should pancreatic cancer surveillance be performed
- Pancreatic cancer surveillance outcomes and disparities

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Identification and Management of Hereditary Pancreatic Cancer Risk

Genetic testing for pancreatic cancer risk syndromes

Pancreatic cancer risk syndromes

Who should undergo pancreatic cancer surveillance

How should pancreatic cancer surveillance be performed

Pancreatic cancer surveillance outcomes and disparities

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Who Should Be Offered Genetic Testing?

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Hereditary Cancer Testing Criteria

NCCN Guidelines Index
Table of Contents
Discussion

TESTING CRITERIA FOR PANCREATIC CANCER SUSCEPTIBILITY GENES
(Specifically *ATM, BRCA1, BRCA2, CDKN2A,* Lynch syndrome genes [*MLH1, MSH2, MSH6, EPCAM*], *PALB2, STK11, and TP53*) (GENE-A)[a,w]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Exocrine pancreatic cancers
  - All individuals diagnosed with exocrine pancreatic cancer[x]
  - First-degree relatives of individuals diagnosed with exocrine pancreatic cancer[y]
- Neuroendocrine pancreatic tumors - NCCN Guidelines for Neuroendocrine and Adrenal Tumors

Criteria met → GENE-1

If testing criteria not met, consider testing criteria for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

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Pathogenic Variants in Unselected PDACs

Gastroenterology 2015;148:556–564

CLINICAL—PANCREAS

Prevalence of Germline Mutations in Cancer Predisposition Genes in Patients With Pancreatic Cancer

Robert C. Grant,[1,2,*] Iris Selander,[3,*] Ashton A. Connor,[4] Shamini Selvarajah,[5] Ayelet Borgida,[3] Laurent Briollais,[3] Gloria M. Petersen,[6] Jordan Lerner-Ellis,[1,5,7] Spring Holter,[3] and Steven Gallinger[1,3,4]

[1]Ontario Institute for Cancer Research, Canada; [2]Department of Medicine, [4]Division of General Surgery, Department of Surgery, University Health Network, [5]Laboratory Medicine and Pathobiology, University of Toronto, Canada; Lunenfeld-Tanenbaum Research Institute, [7]Pathology and Laboratory Medicine, Mount Sinai Hospital, Canada; [6]Department

Short Communication

Prevalence of Pathogenic Mutations in Cancer Predisposition Genes among Pancreatic Cancer Patients

Chunling Hu[1], Steven N. Hart[2], William R. Bamlet[2], Raymond M. Moore[2], Kannabiran Nandakumar[2], Bruce W. Eckloff[3], Yean K. Lee[3], Gloria M. Petersen[4], Robert R. McWilliams[4], and Fergus J. Couch[1,2]

Abstract

The prevalence of germline pathogenic mutations in a comprehensive panel of cancer predisposition genes is not well-defined for patients with pancreatic ductal adenocarcinoma (PDAC). To estimate the frequency of mutations in a panel of 22 cancer predisposition genes, 96 patients unselected for a family history of cancer who were recruited to the Mayo Clinic Pancreatic Cancer patient registry over a 12-month period were screened by next-generation sequencing. Fourteen pathogenic mutations in 13 patients (13.5%) were identified in eight genes: four in *ATM*, two in *BRCA2*, *CHEK2*, and *MSH6*, and one in *BARD1*, *BRCA1*, *FANCM*, and *NBN*. These included nine mutations (9.4%) in established pancreatic cancer genes. Three mutations were found in patient with PDAC, and 10 mutations substantial proportion of patients with PDAC carry germline mutations in predisposition genes associated with other cancers and that a better understanding of pancreatic cancer risk will depend on evaluation of families with broad constellations of tumors. These findings highlight the need for recommendations governing germline gene-panel testing of patients with pancreatic cancer. *Cancer Epidemiol Biomarkers Prev; 25(1); 207–11. ©2015 AACR.*

VOLUME 35 · NUMBER 30 · OCTOBER 20, 2017

JOURNAL OF CLINICAL ONCOLOGY — RAPID COMMUNICATION

Deleterious Germline Mutations in Patients With Apparently Sporadic Pancreatic Adenocarcinoma

Koji Shindo, Jun Yu, Masaya Suenaga, Shahriar Fesharakizadeh, Christy Cho, Anne Macgregor-Das, Abdulrehman Siddiqui, P. Dave Witmer, Koji Tamura, Tae Jun Song, Jose Alejandro Navarro Almario, Aaron Brant, Michael Borges, Madeline Ford, Thomas Barkley, Jin Ho, Matthew J. Weiss, Christopher L. Wolfgang, Nicholas J. Roberts, Ralph H. Hruban, Alison P. Klein, and Michael Goggins

ABSTRACT

Purpose
Deleterious germline mutations contribute to pancreatic cancer susceptibility and are well documented in families in which multiple members have had pancreatic cancer.

Methods
To define the prevalence of these germline mutations in patients with apparently sporadic pancreatic cancer, we sequenced 32 genes, including known pancreatic cancer susceptibility genes, in DNA prepared from normal tissue obtained from 854 patients with pancreatic ductal adenocarcinoma, 288 patients with other pancreatic and periampullary neoplasms, and 51 patients with non-neoplastic diseases who underwent pancreatic resection at Johns Hopkins H 2000 and 2015.

Results
Thirty-three (3.9%; 95% CI, 3.0% to 5.8%) of 854 patients with pancreatic cancer germline mutation, 21 (3.5%) of which affected known familial pancreatic can genes: *BRCA2* (12 patients), *ATM* (10 patients), *BRCA1* (3 patients), *PALB2* (2 p patients), *CDKN2A* (1 patient), and *TP53* (1 patient). Patients with these germline younger than those without (mean ± SD, 60.8 ± 10.6 v 65.1 ± 10.5 years; *P* = germline mutations were also found in *BUB1B* (1) and *BUB3* (1). Only three of thes reported a family history of pancreatic cancer, and most did not have a cancer suggest an inherited cancer syndrome. Five (1.7%) of 288 patients with oth neoplasms also had a deleterious germline mutation.

Conclusion
Germline mutations in pancreatic cancer susceptibility genes are commonly ide with pancreatic cancer without a significant family history of cancer. These delet cancer susceptibility gene mutations, some of which are therapeutically targetable current family history guidelines are the main criteria used to determine the approp testing.

Prospective Study of Germline Genetic Testing in Incide Cases of Pancreatic Adenocarcinoma

Randall Brand, MD[1]; Erkut Borazanci, MD, MS[2]; Virginia Speare, PhD[3]; Beth Dudley, MS, MPH[3]; Eve Karlosk Mary Linton B. Peters, MD, MS[4]; Lindsey Stobie, MS[4]; Nathan Bahary, MD, PhD[1]; Herbert Zeh, MD[5]; Amer Zureik Melissa Hogg, MD[5]; Kenneth Lee, MD[5]; Allan Tsung, MD[5]; John Rhee, MD[1]; James Ohr, DO[1]; Weijing Sun, MD James Lee, MD, PhD[1]; A. James Moser, MD[4]; Kim DeLeonardis, MS[4]; Jill Krejdovsky, MS[4]; Emily Dalton, MS Holly LaDuca, MS[3]; Jill Dolinsky, RN, MS[3]; Arlene Colvin, MS[3]; Cynthia Lim, MS[2]; Mary Helen Black, PhD, MS[3]; Nadine Tung, MD[1]

BACKGROUND: The objective of this study was to investigate the prevalence of pathogenic germline variants (PGVs) in 32 susceptibility genes in individuals with newly diagnosed pancreatic ductal adenocarcinoma (PDAC). A key secondary objec to evaluate how often PGVs would have been undetected with existing genetic testing criteria. **METHODS:** From May 2016 May 2017, this multicenter cohort study enrolled consecutive patients aged 18 to 89 years with histologically confirmed PDA nosed within the previous 12 weeks. Demographics, medical histories, and 3-generation pedigrees were collected from part who provided samples for germline DNA analysis. **RESULTS:** Four hundred nineteen patients were deemed eligible, 302 were and 298 were included in the final cohort. Clinically actionable variants were reported in 29 PDAC patients (9.7%), with 23 (7.7 ing a PGV associated with an increased risk for PDAC. Six of 23 individuals (26%) with PDAC-associated gene mutations did n currently established genetic testing criteria. According to guideline-based genetic testing, only 11 of the 23 PGVs (48%) PDAC genes would have been detected. Six additional patients (2%) had PGVs associated with an increased risk for other **CONCLUSIONS:** These findings support the significant prevalence of PGVs associated with PDAC and the limitations of curre digms for selecting patients for genetic testing, and they thereby lend support for universal germline multigene genetic testi population. *Cancer* **2018;124:3520–27** *© 2018 American Cancer Society.*

Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer

Matthew B. Yurgelun, MD et al.[#]

Purpose: Germline variants in double-strand DNA damage repair (dsDDR) genes (e.g., *BRCA1/2*) predispose to pancreatic adenocarcinoma (PDAC) and may predict sensitivity to platinum-based chemotherapy and poly(ADP) ribose polymerase (PARP) inhibitors. We sought to determine the prevalence and significance of germline cancer susceptibility gene variants in PDAC with paired somatic and survival analyses.

Methods: Using a customized next-generation sequencing panel, germline/somatic DNA was analyzed from 289 patients with resected PDAC ascertained without preselection for high-risk features (e.g., young age, personal/family history). All identified variants were assessed for pathogenicity. Outcomes were analyzed using multivariable-adjusted Cox proportional hazards regression.

Results: We found that 28/289 (9.7%; 95% confidence interval [CI] 6.5–13.7%) patients carried pathogenic/likely pathogenic germline variants, including 21 (7.3%) dsDDR gene variants (3 *BRCA1*, 4 *BRCA2*, 14 other dsDDR genes [*ATM*, *BRIP1*, *CHEK2*, *NBN*, *PALB2*, *RAD50*, *RAD51C*]), 3 Lynch syndrome, and 4 other genes (*APC* p. I1307K, *CDKN2A*, *TP53*). Somatic sequencing and immunohisto-chemistry identified second hits in the tumor in 12/27 (44.4%) patients with germline variants (1 failed sequencing). Compared with noncarriers, patients with germline dsDDR gene variants had superior overall survival (hazard ratio [HR] 0.54; 95% CI 0.30–0.99; *P* = 0.05).

Conclusion: Nearly 10% of PDAC patients harbor germline variants, although the majority lack somatic second hits, the therapeutic significance of which warrants further study.

Genetics in Medicine (2019) 21:213–223; https://doi.org/10.1038/s41436-018-0009-5

Keywords: PARP inhibitors; Familial pancreatic cancer; Lynch syndrome; Hereditary breast and ovarian cancer

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Individuals without Pancreatic Cancer

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Hereditary Cancer Testing Criteria

TESTING CRITERIA FOR PANCREATIC CANCER SUSCEPTIBILITY GENES
(Specifically *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, Lynch syndrome genes [*MLH1*, *MSH2*, *MSH6*, *EPCAM*], PAL

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Exocrine pancreatic cancers
- First-degree relatives of individuals diagnosed with exocrine pancreatic cancer[¥]
- Neuroendocrine pancreatic tumors - NCCN Guidelines for Neuroendocrine and Adrenal Tumors

- Consider genetic risk assessment for individuals who have:
  - Multiple family members with PDAC, even if they are not FDRs
  - Any relative with PDAC and other suggestive family history

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Identification and Management of Hereditary Pancreatic Cancer Risk

Genetic testing for pancreatic cancer risk syndromes

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Commonly Accepted Pancreatic Cancer Susceptibility Genes

- APC
- ATM
- BRCA1
- BRCA2
- CDKN2A
- Mismatch repair genes
  - MLH1, MSH2, MSH6, PMS2, EPCAM
- PALB2
- STK11
- TP53

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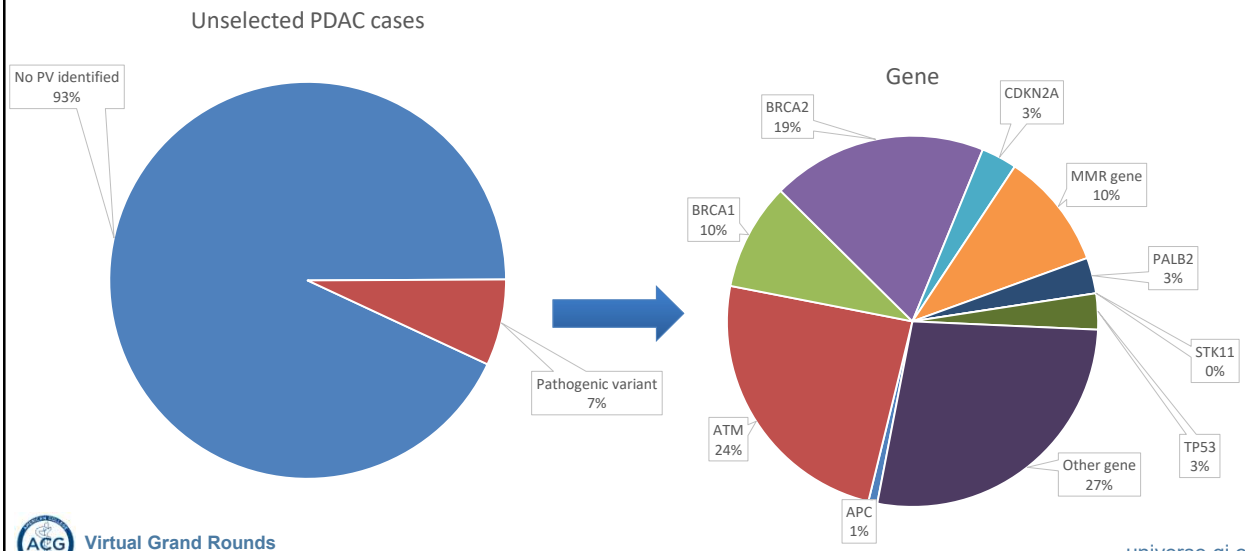
Prevalence Data

-Grant RC et al. Gastroenterology 2015: 148: 556-564.
-Hu C et al. Cancer Epidemiol Biomarkers Prev 2016: 25: 207-211.
-Shindo K et al. J Clin Oncol 2017: 35: 3382-3390.
-Brand R et al. Cancer 2018: 124: 3520-3527.
-Yurgelun MB et al. Genet Med 2019: 21: 213-223.



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Cancer Spectrum and Magnitude of Risk

Pancreatic Cancer Predisposition Genes

Gene	Pancreatic Cancer	Colon Cancer	Gastric Cancer	Small Bowel Cancer	Breast Cancer	Ovarian Cancer	Prostate Cancer	Skin Cancer
APC	●	●	●	●				
ATM	●	●	●		●	●	●	
BRCA1	●				●	●	●	
BRCA2	●				●	●	●	●
CDKN2A	●							●
MMR genes	●	●	●	●		●	●	●
PALB2	●				●	●		
STK11	●	●	●	●	●			
TP53	●	●			●			

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STK11

- Pancreatic cancer risk
  - Relative risk: up to 132
  - Absolute risk: 11% to 36%
- Other findings
  - GI hamartomas
  - Mucocutaneous hyperpigmentation
  - Colon, gastric, and small bowel cancer
  - Breast cancer
  - Lung cancer
  - Gynecologic cancers
  - Sertoli cell tumors of the testes

Gastroenterology 2000; 119: 1447-1453.
Clin Cancer Res 2006; 12(10): 3209-3215.

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CDKN2A

- Pancreatic cancer risk
  - Odds ratio: 12.33
  - Absolute risk: 17%
- Other findings
  - Multiple dysplastic moles
  - Melanoma

JAMA 2018; 319(23): 2401-2409.
Int J Cancer 2000; 87(6): 809-811.

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TP53

- Pancreatic cancer risk
  - Odds ratio: 6.70
- Other findings
  - Sarcomas
  - Breast cancer
  - Brain tumors
  - Adrenocortical carcinoma
  - And so on…

JAMA 2018; 319(23): 2401-2409.

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BRCA2

- Pancreatic cancer risk
  - Relative risk: 3.51
  - Odds ratio: 6.20
- Other findings
  - Breast cancer
  - Ovarian cancer
  - Male breast cancer
  - Prostate cancer

JNCI 1999; 91(15): 1310-1316.
JAMA 2018; 319(23): 2401-2409.

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ATM

- Pancreatic cancer risk
  - Odds ratio: 4.21-5.71
  - Absolute risk: 9.5%
- Other findings
  - Breast cancer
  - Maybe prostate, colon, gastric, ovarian cancers

Cancer Prev Res 2021; 14(4):433-440.
JAMA 2018; 319(23): 2401-2409.
JAMA Oncol 2021; 7(11): 1664-1668.

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Mismatch Repair Genes

- Pancreatic cancer risk
  - Hazard ratio: 8.6
    - MLH1, MSH2, MSH6
  - Odds ratio: 6.66
    - MLH1 only
  - Absolute risk: 6.2%
    - MLH1 only

JAMA 2009; 302(16): 1790-1795.
JAMA 2018; 319(23): 2401-2409.
Gut 2018; 67(7): 1306-1316.

- Other findings
  - Colon cancer
  - Endometrial and ovarian cancers
  - Upper GI cancers
  - Urinary tract cancers
  - Biliary tract cancers
  - Glioblastoma
  - Prostate cancer
  - Sebaceous neoplasms

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BRCA1

- Pancreatic cancer risk
  - Relative risk: 2.26
  - Odds ratio: 2.58
- Other findings
  - Breast cancer
  - Ovarian cancer
  - Male breast cancer
  - Prostate cancer

JNCI 2002; 94(18): 1358-1365.
JAMA 2018; 319(23): 2401-2409.

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PALB2

- Pancreatic cancer risk
  - Relative risk: 2.37
  - Absolute risk: 2% to 3%
- Other findings
  - Breast cancer
  - Ovarian cancer
  - Male breast cancer
  - Prostate cancer

J Clin Oncol 2020; 38(7): 674-685.

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APC

- Pancreatic cancer risk
  - Relative risk: 4.5
  - Absolute risk: 2%
- Other findings
  - Colon polyposis
    - Colon cancer risk up to 100% if untreated
  - Upper GI polyposis
    - Increased risk for gastric cancer and duodenal/ampullary cancer
  - Thyroid cancer
    - Cribriform morular variant of PTC
  - Medulloblastoma
  - Hepatoblastoma

Gut 1993; 34: 1394-1396.

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Familial Pancreatic Cancer

- Definition
  - A family that has at least two individuals with PDAC who are first-degree relatives to each other for whom no genetic cause has been identified

Table 3 *Risk of pancreatic cancer (PC) among members of familial pancreatic cancer (FPC) kindreds stratified by their number of first-degree relatives (FDRs) with pancreatic cancer*

No. of FDRs with PC[a]	No. of individuals	Person-years of follow-up	Observed cases	Expected cases[b]	SIR[c] (95% CI)
3 or more	106	287.2	5	0.156	32.0 (10.4–74.7)
2	634	1597.9	4	0.623	6.4 (1.8–16.4)
1	1253	3388.0	2	0.442	4.5 (0.54–16.3)

[a] Denotes each individual's number of FDRs with pancreatic cancer (*i.e.*, the number of their parents, siblings, and children with pancreatic cancer).
[b] Adjusted for age, sex, and race.
[c] SIR, standardized incidence ratio; CI, confidence interval.

Cancer Res 2004; 64: 2634-2638.

Table 2. Standardized incidence ratios (SIRs) of pancreatic cancer among family members at risk: overall and stratified by family history and smoking status*

Family history	No. of individuals	Person-years of follow-up	Observed cases	Expected cases	SIR* (95% CI)	*P*
Familial						
Overall	3934	16760	29	4.27	6.79 (4.54 to 9.75)	<.001
Three or more first-degree relatives	176	797	8	0.47	17.02 (7.34 to 33.5)	<.001
Two first-degree relatives	1043	4477	7	1.76	3.97 (1.59 to 8.2)	.005
One first-degree relatives	2715	11486	14	2.04	6.86 (3.75 to 11.04)	<.001

J Natl Cancer Inst 2010; 102: 119-126.

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How do we interpret genetic test results?

- Positive
  - Establish appropriate guidelines-based management for other cancers
  - Discuss lifestyle modifications to reduce risk for PDAC
  - Determine if the patient meets guidelines for pancreatic cancer surveillance
- Negative/VUS
  - Follow based on personal and family history
  - Discuss lifestyle modifications to reduce risk for PDAC
  - Determine if the family has FPC

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Identification and Management of Hereditary Pancreatic Cancer Risk

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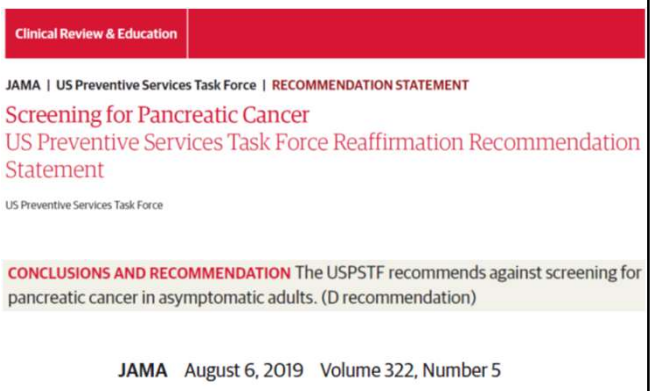
Pancreatic cancer surveillance in the ideal world

In the ideal world pancreatic cancer surveillance should:

1. Allow for earlier detection of a cancer/pre-cancer
2. Permit an intervention (ie surgery) due to earlier detection
3. Improve survival from cancer
4. Not create more harm than good
5. Be cost effective


Clinical Review & Education

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Pancreatic Cancer
US Preventive Services Task Force Reaffirmation Recommendation Statement

US Preventive Services Task Force

CONCLUSIONS AND RECOMMENDATION The USPSTF recommends against screening for pancreatic cancer in asymptomatic adults. (D recommendation)

JAMA August 6, 2019 Volume 322, Number 5

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Who is eligible for pancreatic cancer surveillance?


NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic


Guidelines

Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium

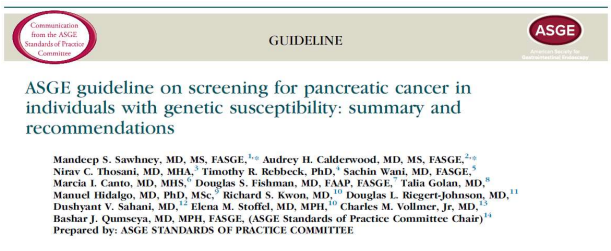
Michael Goggins, Kasper Alexander Overbeek, Randall Brand, Sapna Syngal, Marco Del Chiaro, Detlef K Bartsch, Claudio Bassi, Alfredo Carrato, James Farrell, Elliot K Fishman, Paul Fockens, Thomas M Gress, Jeanin E van Hooft, R H Hruban, Fay Kastrinos, Allison Klein, Anne Marie Lennon, Aimee Lucas, Walter Park, Anil Rustgi, Diane Simeone, Elena Stoffel, Hans F A Vasen, Djuna L Cahen, Marcia Irene Canto, Marco Bruno, International Cancer of the Pancreas Screening (CAPS) consortium


nature publishing group PRACTICE GUIDELINES

CME

ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes

Sapna Syngal, MD, MPH, FACG, Randall E. Brand, MD, FACG, James M. Church, MD, FACG, Francis M. Giardiello, MD, Heather L. Hampel, MS, CGC and Randall W. Burt, MD, FACG


Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE

ASGE guideline on screening for pancreatic cancer in individuals with genetic susceptibility: summary and recommendations

Mandeep S. Sawhney, MD, MS, FASGE, Audrey H. Calderwood, MD, MS, FASGE, Nirav C. Thosani, MD, MHA, Timothy R. Rebbeck, PhD, Sachin Wani, MD, FASGE, Marcia I. Canto, MD, MHS, Douglas S. Fishman, MD, FAAP, FASGE, Talia Golan, MD, Manuel Hidalgo, MD, PhD, MSc, Richard S. Kwon, MD, Douglas L. Riegert-Johnson, MD, Dushyant V. Sahani, MD, Elena M. Stoffel, MD, MPH, Charles M. Vollmer, Jr, MD, Bashar J. Qumseya, MD, MPH, FASGE, (ASGE Standards of Practice Committee Chair)
Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

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Who is eligible for pancreatic cancer surveillance?

Surveillance can be considered:

- Lifetime risk of PDAC close to 5%
- Appropriate age
- Acceptable surgical candidate
- There has been a discussion of the limitations of surveillance
    - Cost
    - High rate of incidental findings
    - Uncertainty about benefits

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Who is eligible for pancreatic cancer surveillance?

Who should undergo surveillance?

Peutz-Jeghers syndrome *(STK11)*
- Age 30 or older

FAMMM (*CDKN2A*)
- Age 40 or older

Hereditary pancreatitis (*PRSS1, SPINK1, CTRC*)
- Age 40 or 20 years after pancreatitis onset

Familial pancreatic cancer
- Two affected relatives who are directly related to one another, with the patient being directly related to at least one of them
- Age 50 or older (or 10 years younger than youngest pancreatic cancer)

***BRCA1/2*, *ATM*, *PALB2*, Lynch syndrome (excluding *PMS2* carriers)**
- Family history of pancreatic cancer in a first or second degree relative
- Age 50 or older (or 10 years younger than youngest pancreatic cancer)

What about surveillance in *BRCA1/BRCA2/ATM/PALB2* carriers without a family history of pancreatic cancer?

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Surveillance in mutation carriers without a family history

Family history can be impacted by:

- Small family size
- Unknown or incorrect family history
- Early deaths due to other cancers/causes, especially in families with hereditary cancer risk syndromes

The majority of pancreatic cancers that develop in *BRCA1/BRCA2/ATM/PALB2* carriers occur in the absence of a family history of pancreatic cancer

Is it right to use family history as eligibility criteria for pancreatic cancer surveillance for *BRCA1/BRCA2/ATM/PALB2* carriers?

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Surveillance in mutation carriers without a family history

Clinical trial of pancreatic cancer surveillance in *BRCA1/BRCA2/PALB2/ATM* carriers without a family history of pancreatic cancer

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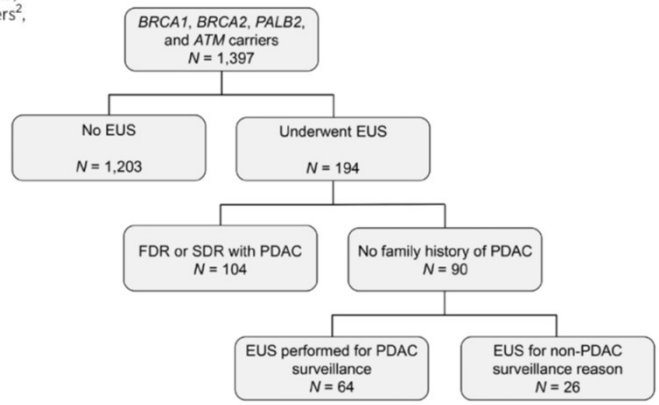
Surveillance in mutation carriers without a family history

CANCER PREVENTION RESEARCH | RESEARCH ARTICLE 2021

EUS-based Pancreatic Cancer Surveillance in *BRCA1/BRCA2/PALB2/ATM* Carriers Without a Family History of Pancreatic Cancer

Bryson W. Katona[1], Jessica M. Long[2], Nuzhat A. Ahmad[1], Sara Attalla[1], Angela R. Bradbury[2], Erica L. Carpenter[2], Dana F. Clark[2], Gillain Constantino[1], Koushik K. Das[3], Susan M. Domchek[2], Christina Dudzik[1], Jessica Ebrahimzadeh[2], Gregory G. Ginsberg[1], Jordan Heiman[1], Michael L. Kochman[1], Kara N. Maxwell[2], Danielle B. McKenna[2], Jacquelyn Powers[2], Payal D. Shah[2], Kirk J. Wangensteen[1], and Anil K. Rustgi[4,5]

- 64 carriers underwent 143 surveillance EUSs
- Median age of 62
- 72% Female
- 73% *BRCA2*, 19% *BRCA1*
- FNA in 5%



39

Surveillance in mutation carriers without a family history

	Total (*N* = 64)	%
EUS findings		
Any abnormality	28	44%
PDAC	2	3%
Mass	3	5%
Cyst	17	27%
Mass/cyst after initial EUS	5	8%
Parenchymal abnormality	10	16%
Heterogeneity	4	6%
Hyperechoic	2	3%
Lobularity	4	6%
Fatty	6	9%
EGD findings		
Any abnormality	26	41%
Esophagitis	8	13%
Esophageal stricture	3	5%
Barrett's esophagus	3	5%
Gastritis	10	16%
Gastric ulcer	2	3%
Gastric intestinal metaplasia	3	5%
Fundic gland polyp[a]	9	14%
Helicobacter pylori	1	2%

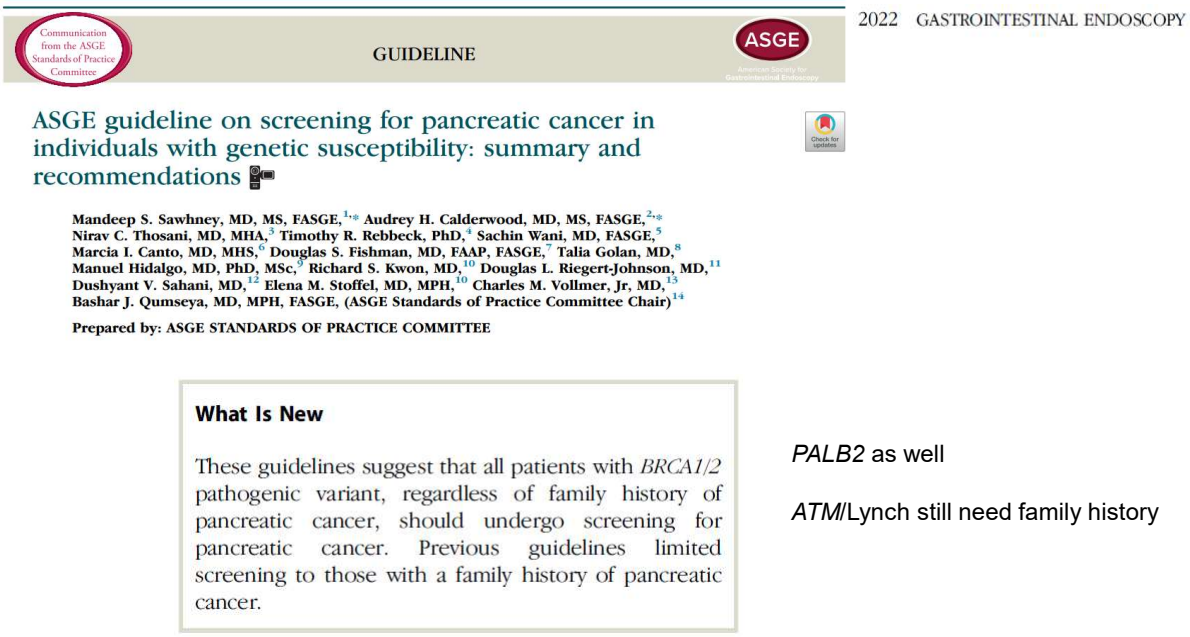
[a]One individual had a fundic gland polyp with low-grade dysplasia.

- PDAC #1 – *BRCA2*, initial EUS at age 58 with 14mm cyst, FNA with HGD, distal pancreatectomy with 0.3cm focus of PDAC.
- PDAC #2 – *BRCA2*, normal yearly EUS from age 72-74, no EUS age 75, EUS age 76 with 3cm PDAC with metastatic disease
- Pancreatic cancer surveillance can be considered in *BRCA1/BRCA2/PALB2/ATM* carriers without a family history of pancreatic cancer
- Effectiveness of this surveillance strategy requires further study

Katona, B.W., et. al., *Cancer Prev Res*, 2021

40

A new shift in the guidelines?



Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE

2022 GASTROINTESTINAL ENDOSCOPY

ASGE guideline on screening for pancreatic cancer in individuals with genetic susceptibility: summary and recommendations

Mandeep S. Sawhney, MD, MS, FASGE,[1,*] Audrey H. Calderwood, MD, MS, FASGE,[2,*] Nirav C. Thosani, MD, MHA,[3] Timothy R. Rebbeck, PhD,[4] Sachin Wani, MD, FASGE,[5] Marcia I. Canto, MD, MHS,[6] Douglas S. Fishman, MD, FAAP, FASGE,[7] Talia Golan, MD,[8] Manuel Hidalgo, MD, PhD, MSc,[9] Richard S. Kwon, MD,[10] Douglas L. Riegert-Johnson, MD,[11] Dushyant V. Sahani, MD,[12] Elena M. Stoffel, MD, MPH,[10] Charles M. Vollmer, Jr, MD,[13] Bashar J. Qumseya, MD, MPH, FASGE, (ASGE Standards of Practice Committee Chair)[14]

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

What Is New

These guidelines suggest that all patients with *BRCA1/2* pathogenic variant, regardless of family history of pancreatic cancer, should undergo screening for pancreatic cancer. Previous guidelines limited screening to those with a family history of pancreatic cancer.

PALB2 as well

ATM/Lynch still need family history

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Identification and Management of Hereditary Pancreatic Cancer Risk

Genetic testing for pancreatic cancer risk syndromes

Pancreatic cancer risk syndromes

Who should undergo pancreatic cancer surveillance

How should pancreatic cancer surveillance be performed

Pancreatic cancer surveillance outcomes and disparities

ACG Virtual Grand Rounds

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How to do pancreatic cancer surveillance

- Imaging
- Blood work
- Enrollment in pancreatic cancer surveillance studies

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How to do pancreatic cancer surveillance

- **Imaging → Performed yearly**
  - MRI or endoscopic ultrasound (EUS)
  - CT and abdominal ultrasound are NOT recommended
- Blood work
- Enrollment in pancreatic cancer surveillance studies

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Comparing imaging methods for pancreatic cancer screening

	Pros	Cons
MRI	Non-invasive Better for cyst detection	If lesion found → need EUS Gadolinium High incidental finding rate (~30%) Expensive
EUS	Allows for sampling of pancreatic lesions Better for solid lesion detection	Invasive and requires sedation Expertise dependent High incidental finding rate (~30%) Expensive

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Comparing imaging methods for pancreatic cancer surveillance

Table 4 Sensitivity of surveillance modalities in detecting pancreatic abnormalities

Abnormality on imaging	Total*, N	EUS	MRI/MRCP	EUS vs MRI/MRCP P value
Solid lesions	25	100% (22/22)	22% (4/18)	<0.001
Indeterminate lesions†	36	61% (22/36)	54% (19/35)	0.85
Cystic lesions	463	42% (187/446)	83% (376/455)	<0.001
≥10 mm	38	70% (26/37)	92% (34/37)	0.06
<10 mm	424	39% (161/409)	82% (342/418)	<0.001
With solid component or mural nodule	5	100% (4/4)	20% (1/5)	0.13
Main pancreatic ducts 5–9 mm‡	21	62% (13/21)	60% (12/20)	>0.99
Pancreatic neuroendocrine tumours	6	100% (6/6)	33% (2/6)	0.13

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Overbeek K.A., et al, *Gut*, 2022

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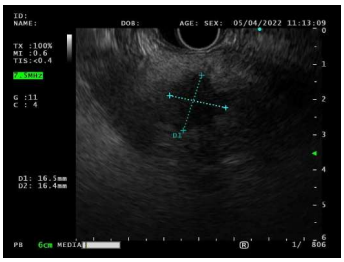
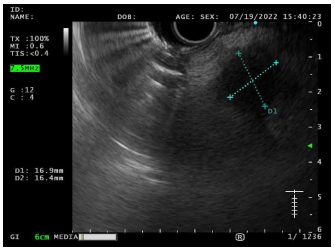
Real world example

- 64 yo M *BRCA2*
- Sister with PDAC at age 62, *BRCA2*+
- EUS (5/2022)
  - **1.6cm solid mass in panc head** → FNA non-diagnostic
  - Multiple pancreatic head cysts
- MRI (5/2022)
  - Multifocal pancreatic cystic lesions with no suspicious features
  - No mass
- MRI (6/2022)
  - 6 cystic lesions in the pancreas (5 in head, largest 1.3cm)
  - No mass
- EUS (7/2022)
  - **Hypoechoic pancreatic head mass, 1.6cm** → FNA non-diagnostic
  - Multiple pancreatic head cysts
- Whipple (8/2022)
  - **Pancreatic adenosquamous carcinoma**
  - **LN negative, Stage 1B**

5/2022



7/2022



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How to do pancreatic cancer surveillance

- Imaging → Performed yearly
- **Blood work**
  - Ca19-9
  - Screen for elevated fasting blood glucose/diabetes (HgbA1C or fasting blood glucose)
  - Galleri
  - IMMray PanCan-d
- Enrollment in pancreatic cancer surveillance studies

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The ideal blood-based biomarkers for early pancreatic cancer detection

- Effective at detecting early stage PDAC
- High sensitivity and specificity
- Affordable
- Multianalyte
- Can be checked likely at least twice per year
- Tested with appropriate control populations (ie pancreatitis)

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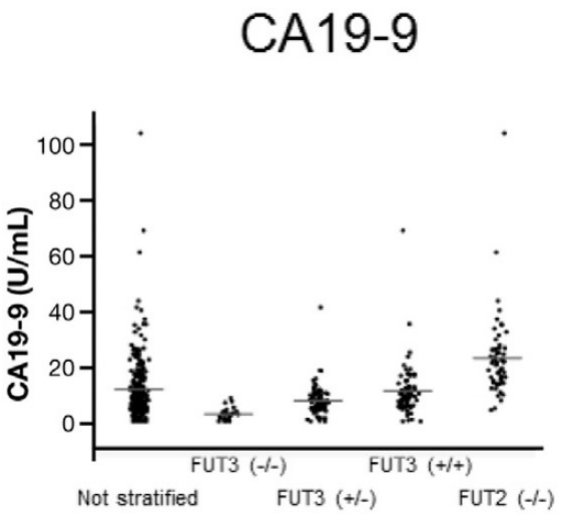
Blood-based tests for pancreatic cancer surveillance

CA19-9

- Data do not support using this as a standalone test
- Disadvantage
  - Varying baseline levels of CA19-9
  - ~10% of the population is Lewis antigen null and does not express CA19-9
- Can consider using genotype-specific CA19-9 "normal ranges"



Abe, T., et. al., *CGH*, 2020

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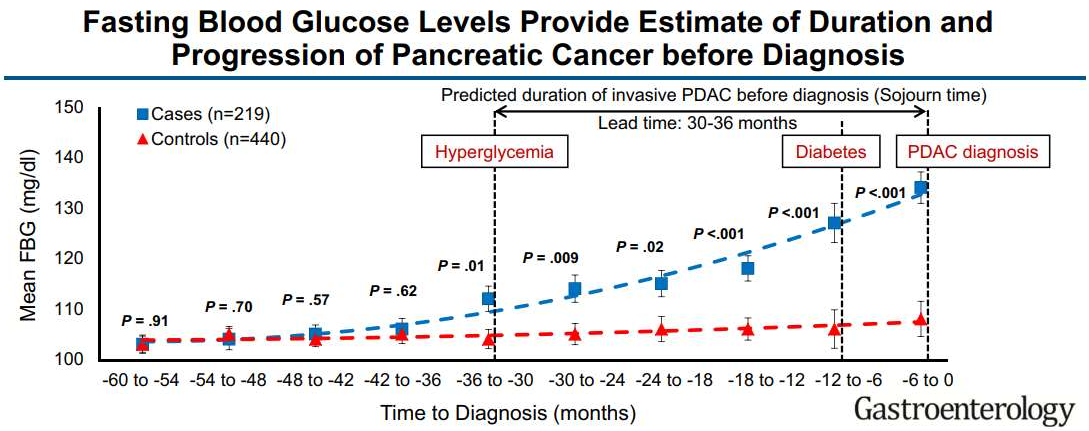
Blood-based tests for pancreatic cancer surveillance



Sharma, A., et. al., *Gastroenterology*, 2018

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Blood-based tests for pancreatic cancer surveillance

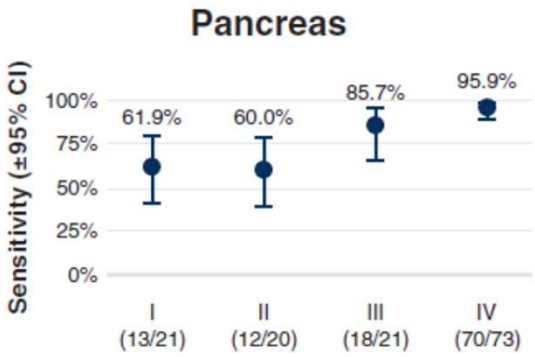
How to incorporate blood glucose into pancreatic cancer surveillance?

- Yearly assessment of fasting blood glucose and/or HgbA1C
- Consider more frequent pancreatic surveillance (q6 months) if:
  - Development of pre-DM/DM
  - DM becomes rapidly more difficult to control

Blood-based tests for pancreatic cancer surveillance

Galleri

ctDNA methylation



galleri.com

Klein, E.A., et. al., *Annals of Oncology*, 2021

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Blood-based tests for pancreatic cancer surveillance

Detection
Adenocarc
Multiplex

Randall E. Brand, MD[1], Ja
Marién Castillo, PhD[6], Ju
Linda Dexlin Mellby, PhD

nd Translational
ROENTEROLOGY

PRESS RELEASE

immunovia

Lund, Sweden, July 11, 2023

Immunovia to Significantly Restructure to Focus Resources on its Next-Generation Blood Test for Pancreatic Cancer Detection

LUND (SWEDEN) – **LUND (SWEDEN)** – Immunovia (Nasdaq Stockholm: IMMNOV), the diagnostics company focused on early detection of pancreatic cancer, today announced plans to restructure its operations. The company will cease commercialization of its IMMray PanCan-d test in the United States to focus its resources on the further development and clinical testing of the Company's promising next generation pancreatic cancer detection test.

Measures 8 pro
CA19-9 assay i

est

using 8-plex
+ CA19-9
d test)

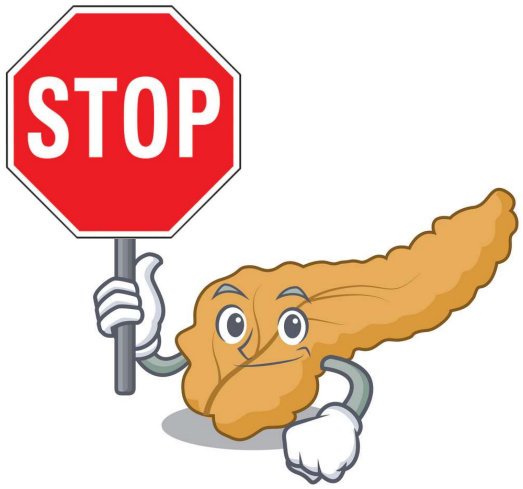
& II): 89%
ges): 92%
Specificity: 99%

531 Total

54

Bottom line on commercial blood-based tests for pancreatic cancer surveillance

- At this time **I would not recommend their regular use** in individuals at high-risk
- Major issues:
  - False positives
    - → extra work-up
    - → worry/stress
  - Cost/lack of insurance coverage
  - Data is still immature



www.vectorstock.com

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How to do pancreatic cancer surveillance

- Imaging → Performed yearly
- Blood work
- **Enrollment in pancreatic cancer surveillance studies**

Pancreatic cancer surveillance studies for high-risk individuals

CAPS-5 Study

(The Cancer of the Pancreas Screening-5 Study)

NIH NATIONAL CANCER INSTITUTE

Institution	City, State
Case Western Reserve University	Cleveland, OH
Columbia University	New York, NY
Dana Farber Cancer Institute/Brigham and Women's Hospital	Boston, MA
Johns Hopkins University	Baltimore, MD
University of Michigan	Ann Arbor, MI
University of Pennsylvania	Philadelphia, PA
University of Pittsburgh	Pittsburgh, PA
Yale University	New Haven, CT

Katona, B.W., et al., *Pancreatology*, 2021

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Pancreatic cancer surveillance studies for high-risk individuals

PRECEDE
The Pancreatic Cancer Early Detection Consortium

project purple
A WORLD WITHOUT PANCREATIC CANCER

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Identification and Management of Hereditary Pancreatic Cancer Risk

Genetic testing for pancreatic cancer risk syndromes

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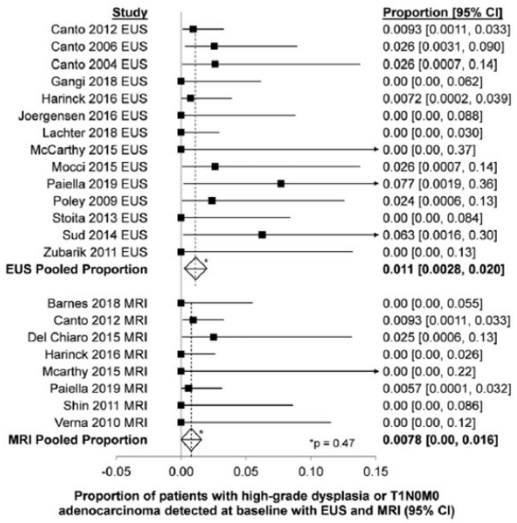
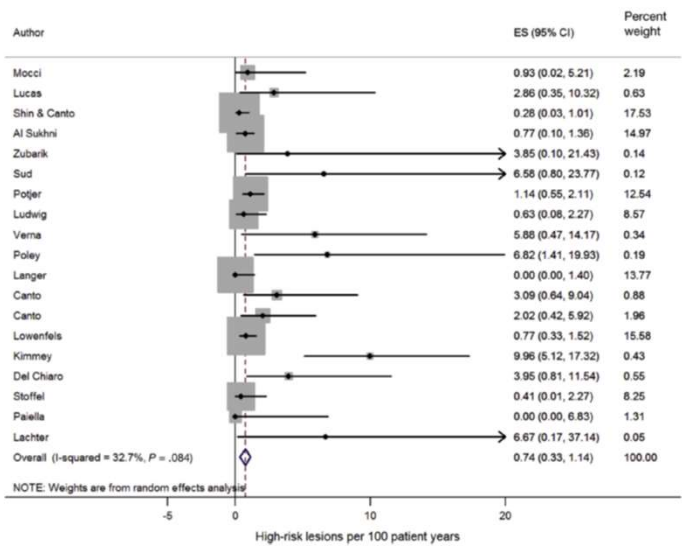
Pancreatic cancer surveillance outcomes



Number needed to screen = 111

Kogekar N, et al, *Pancreatology*, 2020



Number needed to screen = 135

Corral J.E., et al, *CGH*, 2019

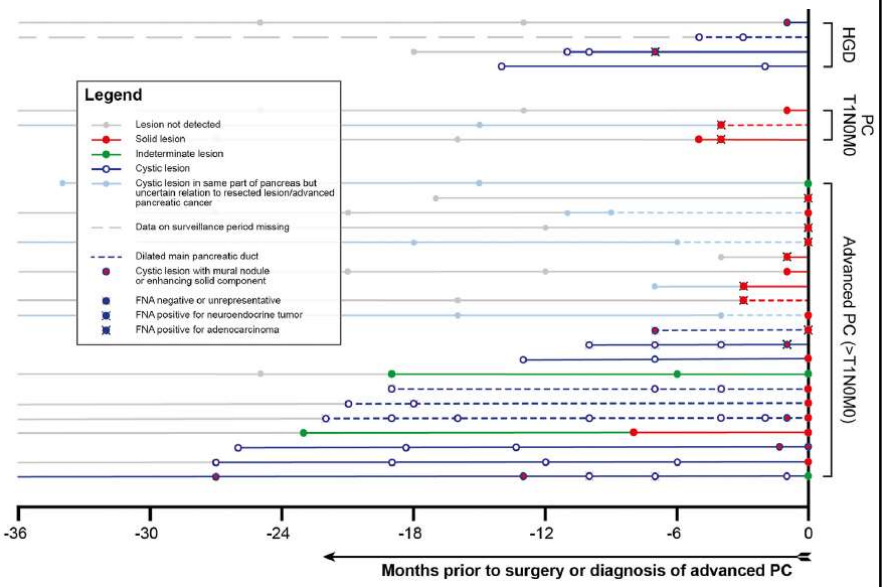
60

Pancreatic cancer surveillance outcomes

28 developed progression to PDAC or HGD during follow-up

46% presented with a new lesion
- Median of 11 months after prior exam
- 77% had progressed beyond the pancreas

54% had a lesions with neoplastic progression
- Primarily cystic
- 73% had progressed beyond the pancreas



Overbeek, K.A., et al, *Gastroenterology*, 2022

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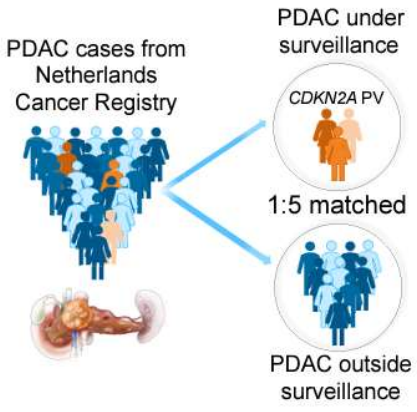
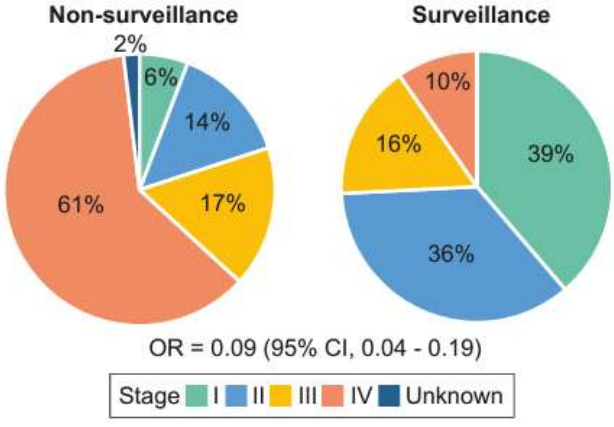
Pancreatic cancer surveillance outcomes





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Klatte D.C.F., et al, *Gastroenterology*, 2023

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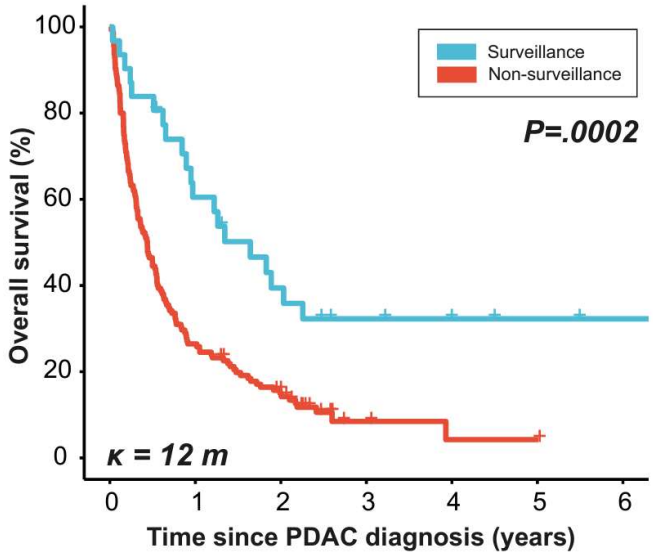
Pancreatic cancer surveillance outcomes



Klatte D.C.F., et al, *Gastroenterology*, 2023

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Pancreatic cancer surveillance outcomes

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

Journal of Clinical Oncology®

Mohamad Dbouk, MD[1]; Bryson W. Katona, MD[2]; Randall E. Brand, MD[3]; Amitabh Chak, MD, PhD[4]; Sapna Syngal, MD[5,6]; James J. Farrell, MD[7]; Fay Kastrinos, MD[8]; Elena M. Stoffel, MD[9]; Amanda L. Blackford, MS[10]; Anil K. Rustgi, MD, PhD[7]; Beth Dudley, MS[3]; Linda S. Lee, MD[5,6]; Ankit Chhoda, MD[7]; Richard Kwon, MD[9]; Gregory G. Ginsberg, MD[2]; Alison P. Klein, PhD, MHS[1,10,11,12]; Ihab Kamel, MD[10,13]; Ralph H. Hruban, MD[1,10]; Jin He, MD, PhD[10,14]; Eun Ji Shin, MD, PhD[11]; Anne Marie Lennon, MB, PhD[10,11,13,14]; Marcia Irene Canto, MD, MHS[10,11]; and Michael Goggins, MB, MD[1,10,11]

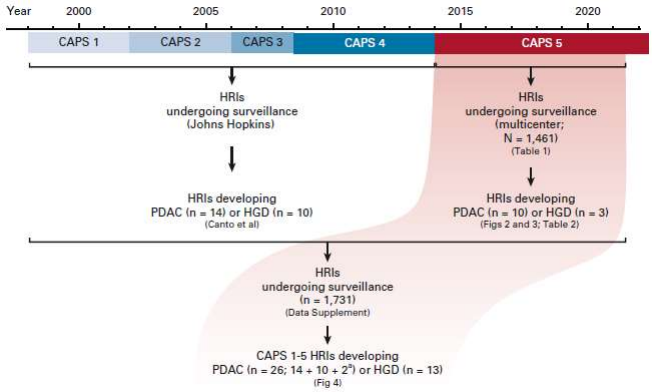

TABLE 1. Baseline Characteristics of the Cancer of Pancreas Screening-5 Study Cohort

High-Risk Cohort	N = 1,461
Age, mean ± SD, years	60.3 ± 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)

Dbouk M., Katona B.W., et al, *JCO*, 2022

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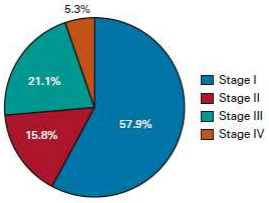
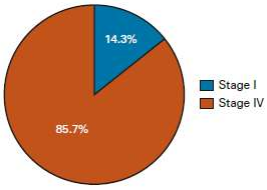
Pancreatic cancer surveillance outcomes

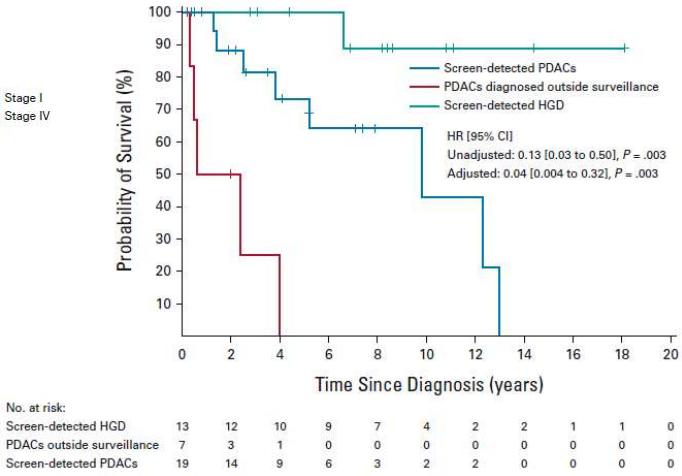
PDACs detected during surveillance



PDACs detected outside of surveillance



	Detected during surveillance	Detected outside surveillance
Median survival	9.8 years	1.5 years
5-year survival	73.3%	0%



Dbouk M., Katona B.W., et al, *JCO*, 2022

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Lack of diversity in the PDAC surveillance outcome literature

Study	Year published	Number of participants	White	Women	Location
Dbouk, et al., *JCO* (CAPS5)	2022	1461	94.5%	64.6%	8 US centers
Overbeek, et al., *Gut*	2022	366	Not reported	57%	Netherlands
Klatte, et al., *JCO*	2022	347	Not reported	58%	Netherlands
Overbeek, et al., *Gastroenterology* (International CAPS)	2022	122 (out of 2552)	96.7%	58%	16 international centers

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Disparities in PDAC surveillance study enrollment

CANCER PREVENTION RESEARCH | RESEARCH ARTICLE

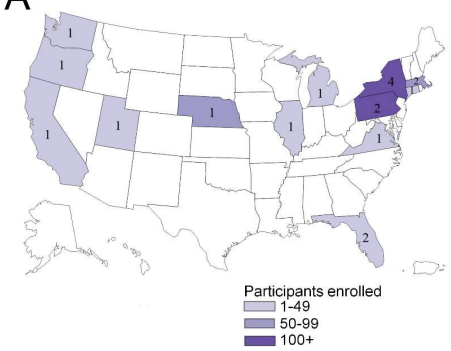
Racial, Ethnic, and Sex-based Disparities among High-risk Individuals Undergoing Pancreatic Cancer Surveillance

Bryson W. Katona[1], Kelsey Klute[2], Randall E. Brand[3], Jessica N. Everett[4], James J. Farrell[5], Kieran Hawthorne[6], Vivek Kaul[7], Sonia S. Kupfer[8], Salvatore Paiella[9], Diane M. Simeone[4], Daniel A. Sussman[10], George Zogopoulos[11], Aimee L. Lucas[12], and Fay Kastrinos[13]; the PRECEDE Consortium

Cancer Prev Res; 2023

1113 high-risk individuals enrolled between May 2020 and March 2022

A



B

Center	City	Country
British Columbia Cancer Agency	Vancouver, BC	Canada
McGill University Health Centre	Montreal, QC	Canada
Sheba Medical Center	Tel Aviv	Israel
Azienda Ospedaliera Universitaria Integrata Verona	Verona	Italy
Instituto Ramón y Cajal de Investigación Sanitaria	Madrid	Spain
Columbia University Irving Medical Center	New York, NY	US
Huntsman Cancer Institute	Salt Lake City, UT	US
Inova Schar	Fairfax, VA	US
Massachusetts General Hospital/Harvard University	Boston, MA	US
Mayo Clinic Florida	Jacksonville, FL	US
Mt. Sinai School of Medicine	New York, NY	US
New York University Langone Health	New York, NY	US
Oregon Health & Science University	Portland, OR	US
UC San Diego Moores Cancer Center	San Diego, CA	US
UMass Memorial Medical Center	Worcester, MA	US
University of Chicago Medicine	Chicago, IL	US
University of Miami	Miami, FL	US
University of Michigan	Ann Arbor, MI	US
University of Nebraska Medical Center	Omaha, NE	US
University of Pennsylvania	Philadelphia, PA	US
University of Pittsburgh Medical Center	Pittsburgh, PA	US
University of Rochester Medical Center	Rochester, NY	US
University of Washington/Fred Hutchinson	Seattle, WA	US
Yale University	New Haven, CT	US

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Disparities in PDAC surveillance study enrollment

Table 1. Baseline characteristics of HRIs enrolled in the PRECEDE Consortium.

Variables		*N* for each variable	*n* (%) or median (range)
High-risk subgroup	FPC	1,113	525 (47.2%)
	Gene + FHx		505 (45.4%)
	FAMMM		63 (5.7%)
	PJS		18 (1.6%)
	HP		2 (0.2%)
Site country	US	1,113	921 (82.7%)
	Canada		90 (8.1%)
	Spain		6 (0.5%)
	Israel		17 (1.5%)
	Italy		79 (7.1%)
Age at consent (years)		1,113	61 (27, 85)
	<50		141 (12.7%)
	50–59		367 (33%)
	60–69		416 (37.4%)
	70–79		168 (15.1%)
	80+		21 (1.9%)
Sex	Male	1,113	373 (33.5%)
	Female		734 (65.9%)
	Unknown		6 (0.5%)
Race	White	1,113	976 (87.7%)
	Black		22 (2%)
	Asian		7 (0.6%)
	Other		67 (6%)
	Multiracial		9 (0.8%)
	Unknown		32 (2.9%)
Ethnicity	Non-Hispanic	1,113	1050 (94.3%)
	Hispanic		32 (2.9%)
	Unknown		31 (2.8%)
Ashkenazi Jewish descent	No	1,113	765 (68.7%)
	Yes		204 (18.3%)
	Unknown		144 (12.9%)
Pathogenic variant in PDAC risk gene	No	1,113	386 (34.7%)
	Yes		588 (52.8%)
	Unknown		139 (12.5%)

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Katona, B.W., et al., *Cancer Prevention Research*, 2023

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Disparities in PDAC surveillance study enrollment

Table 4. Consent and biosample collection rates among HRIs stratified by race.

Variable		Total		White		Black		Asian		Other		Multiracial		P
		N for each variable	*n* (%) or median (range)	*N* for each variable	*n* (%) or median (range)	*N* for each variable	*n* (%) or median (range)	*N* for each variable	*n* (%) or median (range)	*N* for each variable	*n* (%) or median (range)	*N* for each variable	*n* (%) or median (range)	
Consent to imaging		1,113	1,108 (99.6%)	976	972 (99.6%)	22	22 (100.0%)	7	7 (100.0%)	67	66 (98.5%)	9	9 (100.0%)	0.401
First type of imaging after enrollment	EUS	656	408 (62.2%)	575	381 (66.3%)	12	8 (66.7%)	6	4 (66.7%)	43	5 (11.6%)	4	3 (75.0%)	<0.001
	MRI		248 (37.8%)		194 (33.7%)		4 (33.3%)		2 (33.3%)		38 (88.4%)		1 (25.0%)	
Consent for DNA collection		1,113	1,087 (97.7%)	976	953 (97.6%)	22	22 (100.0%)	7	7 (100.0%)	67	67 (100.0%)	9	9 (100.0%)	0.736
DNA collected		1,087	804 (74%)	953	698 (73.2%)	22	18 (81.8%)	7	4 (57.1%)	67	59 (88.1%)	9	7 (77.8%)	0.037
Consent for biosample collection		1,113	1,107 (99.5%)	976	971 (99.5%)	22	22 (100.0%)	7	7 (100.0%)	67	67 (100.0%)	9	9 (100.0%)	1.000
Baseline serum collected		1,107	772 (69.7%)	971	677 (69.7%)	22	16 (72.7%)	7	4 (57.1%)	67	48 (71.6%)	9	7 (77.8%)	0.916
Baseline plasma collected		1,107	773 (69.8%)	971	678 (69.8%)	22	16 (72.7%)	7	4 (57.1%)	67	48 (71.6%)	9	7 (77.8%)	0.917

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Identification and Management of Hereditary Pancreatic Cancer Risk

Genetic testing for pancreatic cancer risk syndromes

Pancreatic cancer risk syndromes

Who should undergo pancreatic cancer surveillance

How should pancreatic cancer surveillance be performed

Pancreatic cancer surveillance outcomes and disparities

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Take home points

- Genetic testing should be offered to all individuals with pancreatic adenocarcinoma, or to their first-degree relatives if the affected family member is unavailable for testing
- Thirteen cancer susceptibility genes have been associated with an increased risk for pancreatic cancer
  - These genes are also associated with increased risks for other cancers
  - The cancer spectrum and magnitude of risk varies by gene
- Pancreatic cancer surveillance should be considered in eligible individuals if patients are agreeable after discussion of the risks, benefits, and limitations
- Pancreatic cancer surveillance should include at least annual imaging of the pancreas with EUS or MRI, as well as at least annual assessment of fasting blood glucose and/or HgbA1C
- All individuals undergoing pancreatic cancer surveillance should be enrolled in clinical studies
- More research is needed focused on optimal surveillance strategies, biomarker development, improved imaging technology, and better risk stratification

Thank you!

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Questions?

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