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Pancreatic Cancer and Malignant Melanoma:

New Insights on Susceptibility and *CDKN2A*

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April 18, 2020 – Clinical Cancer Genetics and Genomics Conference, Chicago

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Disclosures

- None

Pancreatic Cancer in US since 2000

Source: American Cancer Society Cancer Facts and Figures

Year	New cases	Deaths
2000	28,300	28,200
2002	30,300	29,700
2004	31,860	31,270
2006	33,730	32,300
2008	37,680	34,290
2010	43,140	36,800
2012	43,920	37,390
2014	46,420	39,590
2016	53,070	41,780
2018	55,440	44,330
2020	57,600	47,050

(↑100%)

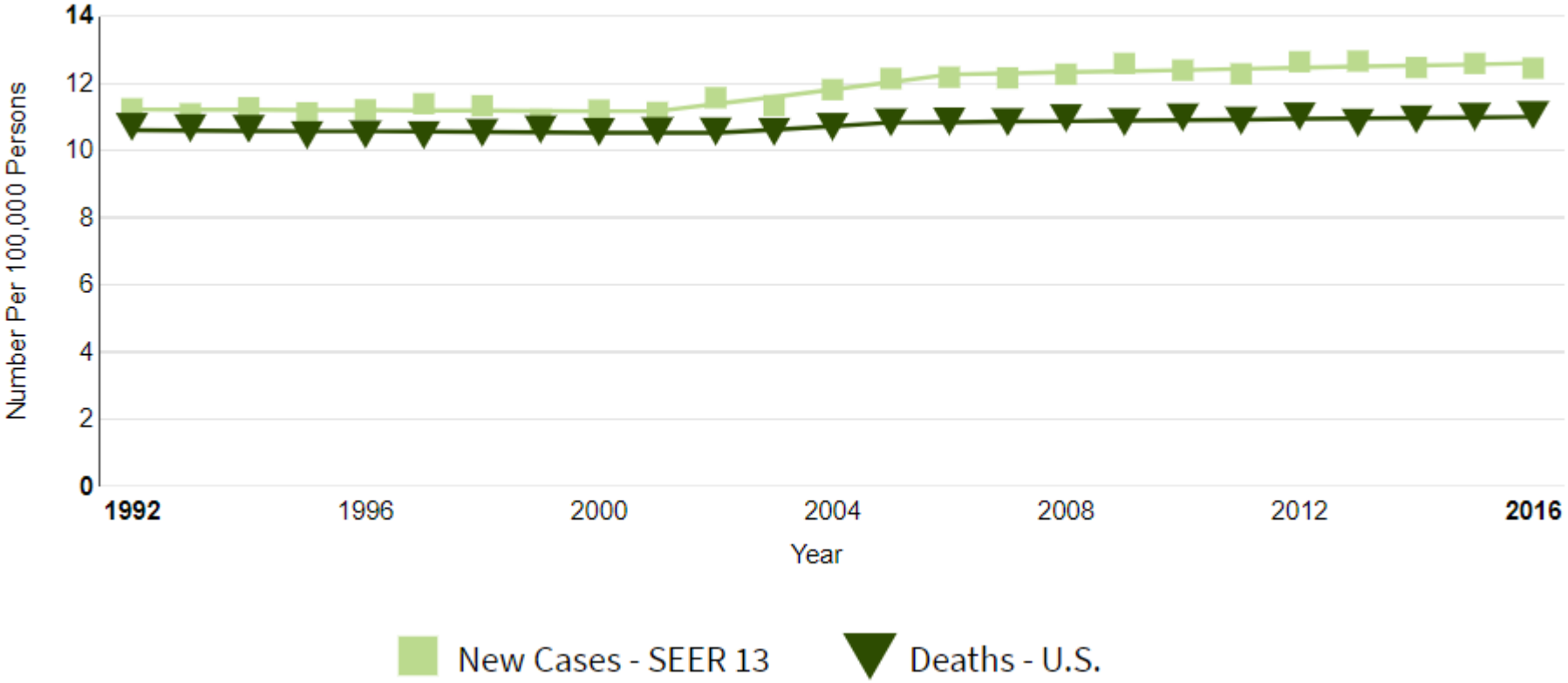
5-year survival: ~5%

In 2020:

- 3% of all new cancers
- 8% of all cancer deaths

5-year survival: 9.8%

Trends in new cases, deaths, 1992-2016



SEER Incidence & U.S. Mortality, All Races, Both Sexes, Rates are Age-Adjusted

- **Incidence: 12.9 /100,000 men and women/ year**
- **Mortality: 11.0 / 100,000 men and women/ year**
- **Lifetime Risk: ~ 1.6 %**

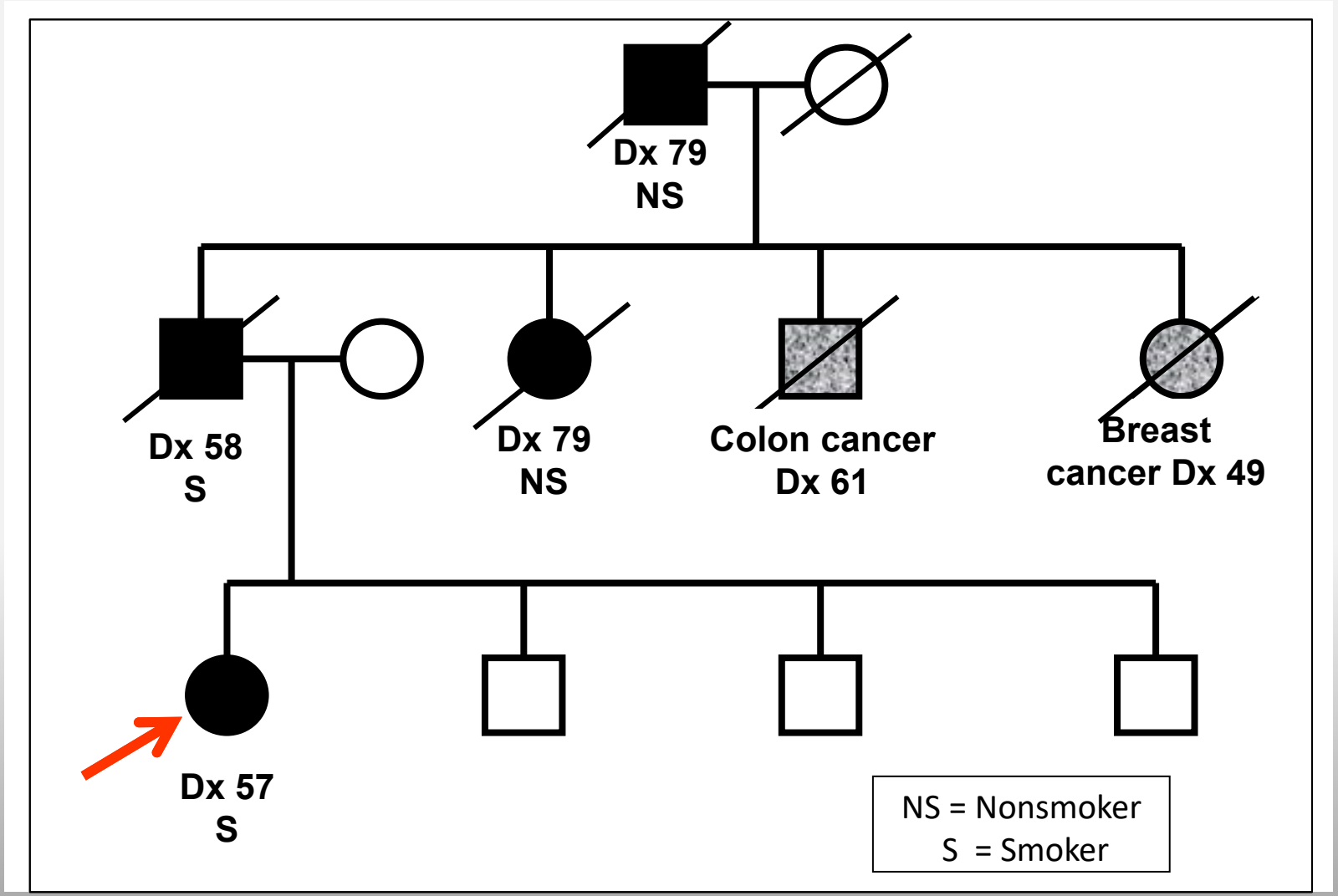
(Age-adjusted, based on 2010-2014 data)

Factors that Increase Pancreatic Cancer Risk

Age	Most occur in people over the age of 60; median age is 71
Being male	More men than women are diagnosed (incidence rates 13.7 vs 10.7 per 100,000)
Smoking	2 to 3 -fold risk vs. nonsmokers
Family History 	2 to 3 -fold risk vs. controls
Race	Black vs White (incidence rates 17.1 vs 13.8 per 100,000)
High BMI, Obesity	2 -fold risk
Hx Diabetes	Longstanding DM 2 to 3- fold risk
Hx Chronic Pancreatitis	5 -fold risk
Heavy alcohol use	1.2 to 1.4 -fold risk

Antwi SO, Jansen RJ, Petersen GM, Cancer of the Pancreas, in Schottenfeld & Fraumeni Cancer Epidemiology and Prevention; Oxford, 2017.

Familial Pancreatic Cancer



Genes and syndromes associated with pancreatic cancer

Gene	Predisposition syndrome	Associated Malignancies
ATM	Familial breast cancer	Breast
BRCA1	Hereditary breast and ovarian cancer	Breast (particularly premenopausal), ovary, male breast, prostate
BRCA2		Breast (particularly premenopausal), ovary, male breast, prostate, melanoma
CDKN2A	Familial atypical mole and malignant melanoma (FAMMM)	Malignant melanoma
Mismatch repair: ***MLH1, MSH2, MSH6, PMS2***	Hereditary nonpolyposis colorectal cancer (Lynch syndrome)	Colorectum, endometrial, ovary, stomach, small bowel, urinary tract (ureter, renal pelvis) biliary, glioblastoma, skin (sebaceous)
PALB2	Familial breast cancer	Fanconi anemia, breast, esophagus, prostate, stomach
PRSS1; SPINK1	Hereditary pancreatitis	--
STK11 (LKB1)	Peutz Jeghers syndrome	Colorectum, small bowel, stomach, breast, gynecologic

Petersen GM. Familial pancreatic cancer. Semin Oncol. 2016 Oct;43(5):548-553.

CDKN2A (chr 9p21)

- Encodes the p16 protein, an important cell cycle regulator and tumor suppressor.
- Is among the most common somatically mutated genes in pancreatic cancer
- Frequent somatic mutations occur in melanoma
- Germline mutations associated with FAMMM

Cutaneous Malignant Melanoma

- Family history of melanoma among:
  - melanoma patients: 7–15%
  - pancreatic cancer patients: 9.2%
- 45% of familial melanomas are associated with germline mutations in *CDKN2A* or *CDK4* (chr 12q14).
- Sun exposure experiences shared among family members is relevant to family history reporting
- *CDKN2A* mutation penetrance varies by geography, by ages 50 to 80 are 30–91% in Australia, 50–76% in the US, and 13–58% in Europe.
- Lower age of onset of melanoma in *CDKN2A* melanoma families

Pancreatic Cancer in FAMMM: *CDKN2A*

- **Pancreatic cancer is the second most commonly observed malignancy in FAMMM patients harboring a *CDKN2A* mutation. Risk of pancreatic cancer 38-fold.**
- **28% of *CDKN2A*-mutation positive families ascertained through melanoma develop pancreatic cancer vs 6% in CDKN2A-mutation negative melanoma families**
- **Estimated risk of pancreatic cancer for *CDKN2A* carriers is 17% by age 75 when ascertained through melanoma; and 15-35% when ascertained through pancreatic cancer**

Pancreatic Cancer and *CDKN2A*

- **Methods:**
  - **1,537 pancreatic adenocarcinoma patients**
  - **Consecutive, unselected white non-Hispanic patients**
  - **Lymphocyte DNA; exons and splice sites sequenced for *CDKN2A***

- **Results:**
  - **9 (0.6%) carried germline mutations in *CDKN2A***
  - **3 mutations previously unreported: missense mutation in p14 (A120P) and two frameshift mutations that affect both p16 and p14ARF (R80fs/ P135fs and V95fs/ G150fs)**
  - ***CDKN2A* mutation carriers were more likely to have:**
    - **family hx pancreatic cancer (p= 0.003); carrier rate 3.3%**
    - **family hx melanoma (p= 0.03); carrier rate 5.3%**
    - **personal hx melanoma (p= 0.01)**

McWilliams RR et al. Eur J Hum Genetics, 2011 Apr;19(4):472-8.

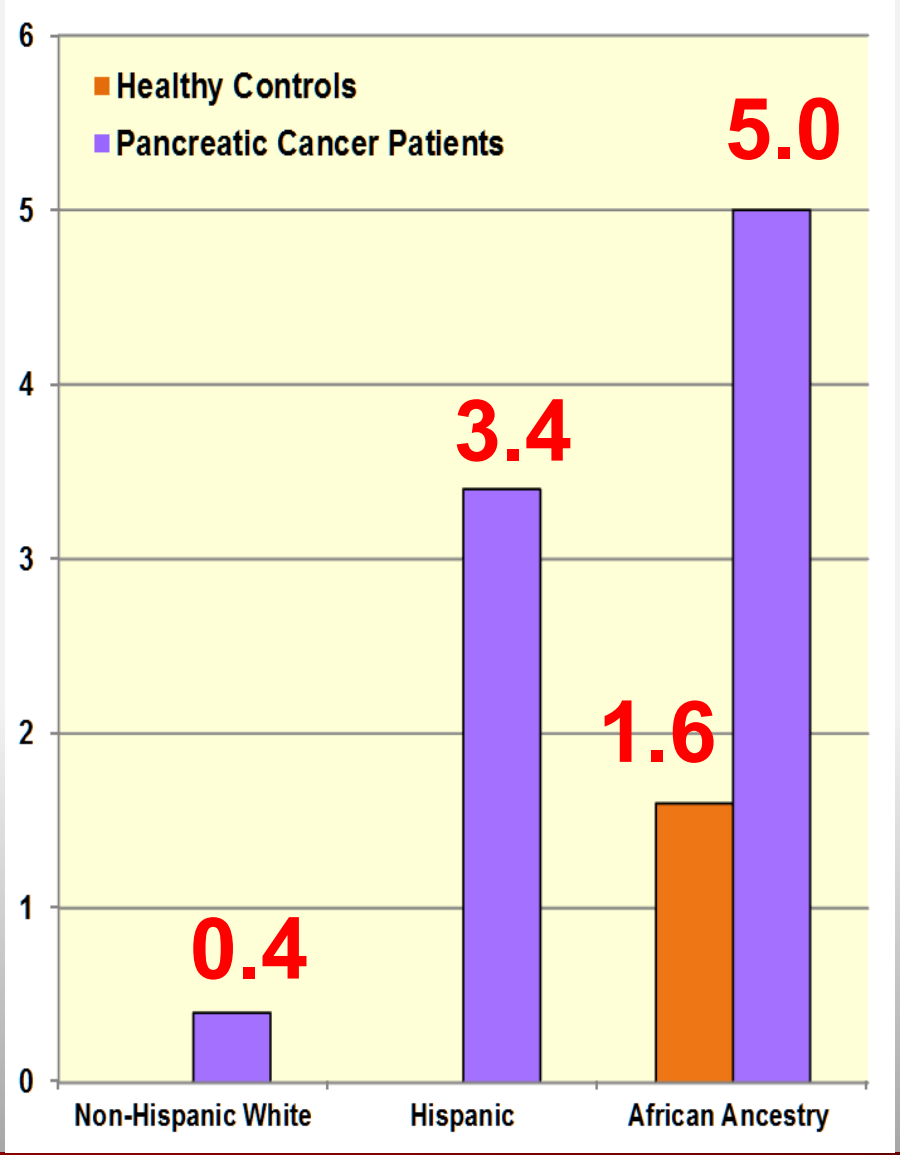
Germline Mutations in *CDKN2A* Among 1,537 Unselected Unrelated Pancreatic Cancer Patients

Patient	Sex/ Age*	Family history of pancreatic cancer	Family history of melanoma	Personal history of melanoma	Exon	Protein	Genetic change	Protein change	Function
1	F 61	Yes	No	No	1A	p16	-34G>T	N/A	Initiation codon
2	M 74	No	Yes	Yes	1A	p16	47T>G	L16>R	AAC p16
3	F 65	No	No	No	1A	p16	71G>C	R24>P	AAC p16
4	F 58	No	No	No	2	p16 p14	192G>C 358G>C	L64>L A120>P	AAC p14ARF
5	M 66	No	No	No	2	p16 p14	238-251 del 404-417 del	R80fs P135fs	makes a hybrid p16/p14 protein after frameshift
6	M 65	Yes	No	No	2	p16 p14	283 del 449 del	V95fs G150fs	frameshift
7	M 45	No	No	No	2	p16 p14	318G>A 484G>A	V106>V A162>T	AAC p14ARF
8	M 67	No	Yes	Yes	2	p16	457G>T	D153spl	Affects splicing in p16/p14ARF
9	M 57	Yes	No	No	2	p16	457G>T	D153spl	Affects splicing in p16/p14ARF

*Male = F=female, Age (years) at diagnosis of pancreatic cancer, AAC = amino acid change

McWilliams RR et al. Eur J Hum Genetics, 2011 Apr;19(4):472-8.

Prevalence of *CDKN2A* germline mutations in populations



Risk is increased for *CDKN2A* mutation carriers

African ancestry	3.3-fold
Hispanic ethnicity	4.6-fold

Compared to non-Hispanic White pancreatic cancer patients:

African ancestry	13.4-fold
Hispanic ethnicity	8.9-fold

***CDKN2A* mutations may account for 25% of the observed excess risk of pancreatic cancer in African Americans**

#controls/cases 1537 58/119 1083/220

Antwi SO et al. Cancer Epi Biomarkers Prev 27:1364-70, 2018

Mayo Clinic study: 25-gene panel testing in familial probands

(Chaffee KG et al. Prevalence of germline mutations among pancreatic cancer patients with positive family history. Genetics in Medicine, July 2017.)

	FPC (n=186)		Non-FPC (n=117)		Total (n=303)	
	N	%	N	%	N	%
All Genes	**24**	**12.9**	**11**	**9.4**	**35**	**11.6**
Genes Associated with PDAC						
ATM	6	3.2	2	1.7	8	2.6
BRCA1	2	1.1	0	0	2	0.7
BRCA2	8	4.3	3	2.6	11	3.6
CDKN2A (p16)	4	2.2	0	0	4	1.3
PALB2	1	0.5	0	0	1	0.3
PMS2	1	0.5	0	0	1	0.3
Genes Not Previously Associated with PDAC						
BARD1	1	0.5	0	0	1	0.3
CHEK2	1	0.5	3	2.6	4	1.3
MUTYH/MYH	0	0	3	2.6	3	1.0
NBN	1	0.5	0	0	1	0.3

Genes with no pathogenic variants: *APC, BMPR1A, BRIP1, CDH1, CDK4, EPCAM/TACSTD 1, MLH1, MSH2, MSH6, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53.*

*** One FPC case carried two pathogenic variants: one in *BRCA1* and one in *BRCA2*.**

Germline mutation prevalences stratified by deleterious/ suspected deleterious and variants of uncertain significance among probands from Familial Pancreatic Cancer (FPC) kindreds, and probands from kindreds not meeting FPC definition. Results shown for probands who were tested for all four genes (total n=716).

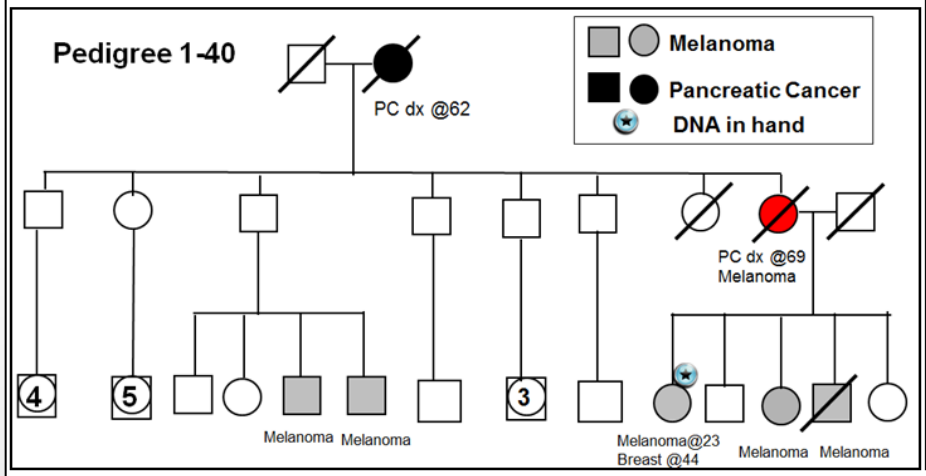
	Deleterious/Suspected Deleterious Mutations n (%)			Variants of Uncertain Significance n (%)		
Gene	FPC (n=515)	Non-FPC (n=201)	Total (n=716)	FPC (n=515)	Non-FPC (n=201)	Total (n=716)
BRCA1	6 (1.2)	0 (0.0)	6 (0.8)	3 (0.6)	0 (0.0)	3 (0.4)
BRCA2	19 (3.7)	6 (3.0)	25 (3.5)	2 (0.4)	1 (0.5)	3 (0.4)
PALB2	3 (0.6)	1 (0.5)	4 (0.6)	11 (2.1)	5 (2.5)	16 (2.2)
CDKN2A	13 (2.5)	0 (0.0)	13 (1.8)	10 (1.9)	3 (1.5)	13 (1.8)
Total	41 (8.0)	7 (3.5)	48 (6.7)	26 (5.0)	9 (4.5)	35 (4.9)

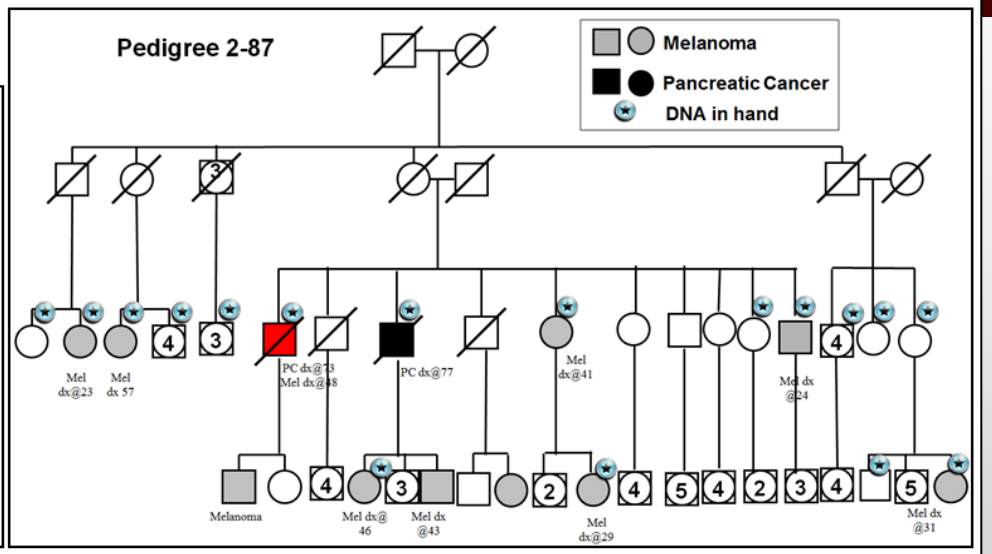
L16R classified as a VUS or deleterious

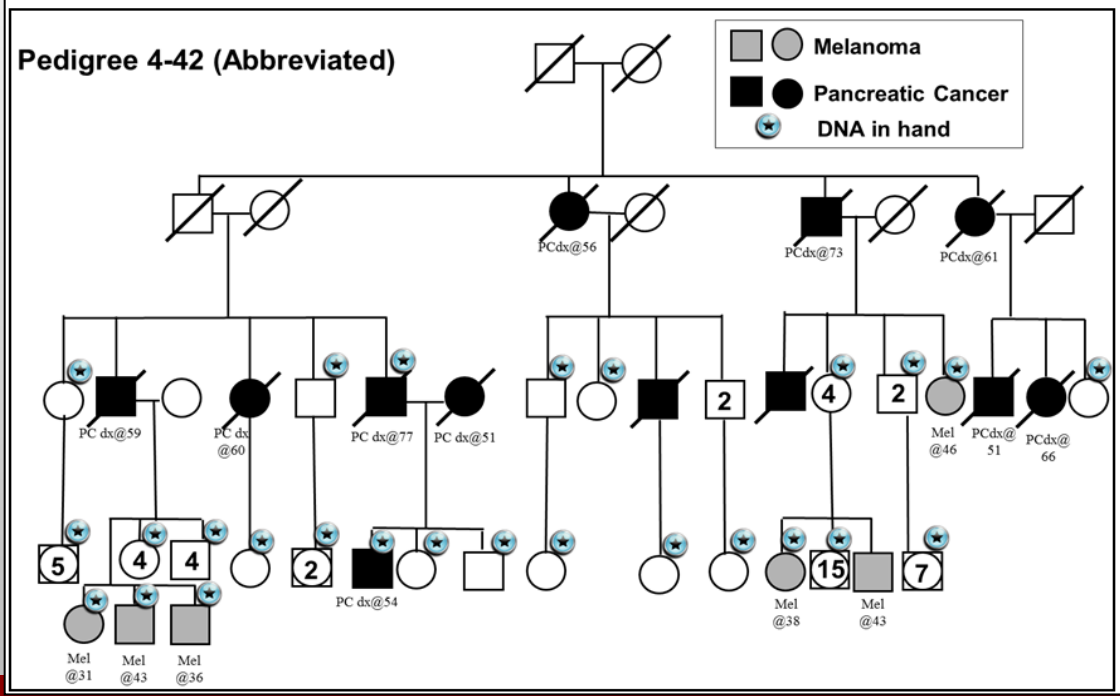
Table 2 Germ-line mutations and counts in 727 sequenced pancreatic cancer probands with positive family history

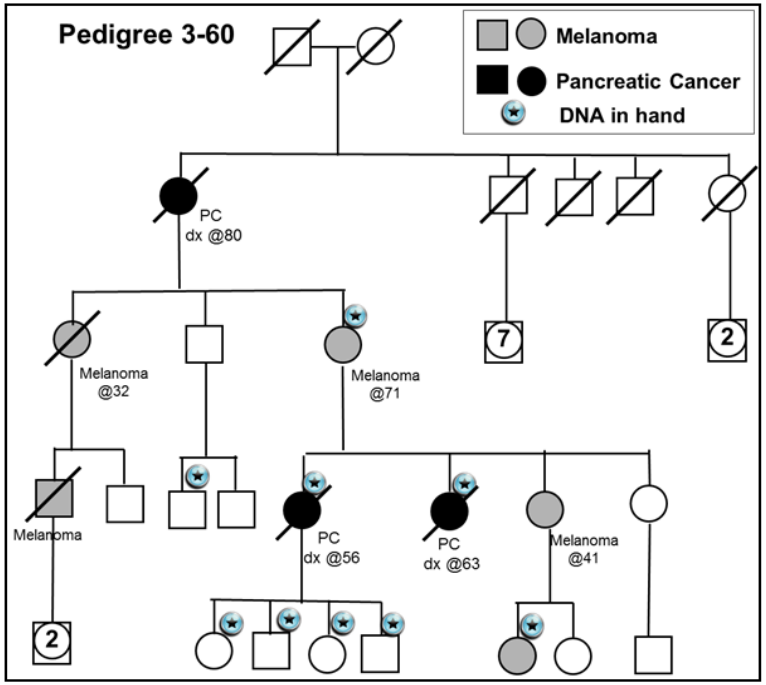
Gene	Deleterious mutations	Variants of uncertain significance	Single-nucleotide polymorphisms
CDKN2A	131insAA	5'UTR-25C>T	None
	225del19		
	286delG		
	32ins24 (in-frame ins)		
	5'UTR-34G>T		
	D153Y (457G>T)		
	G101W (301G>T)	5'UTR-33G>C (*n* = 5)	
	M53I (159G>A)	**G101R (301G>A)**	
	M53I (159G>C)	L16R (47T>G) (*n* = 3)	
	Q50X (148C>T) (*n* = 2)	**L65P (194T>C)**	
	R24P (71G>C)	Q50R (149A>G)	
	V126D (377T>A) (*n* = 2)	**T18P (52A>C)**	

Figure 2. Pedigrees likely due to a founder *CDKN2A* mutation (L16R) ascertained through familial pancreatic cancer.









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

JAMA | Original Investigation

Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer

Chunling Hu, MD, PhD; Steven N. Hart, PhD; Eric C. Polley, PhD; Rohan Gnanaolivu, BS; Hermela Shimelis, PhD; Kun Y. Lee, PhD; Jenna Lilyquist, PhD; Jie Na, MS; Raymond Moore, BS; Samuel O. Antwi, PhD; William R. Bamlet, MS; Kari G. Chaffee, MS; John DiCarlo, PhD; Zhong Wu, PhD; Raed Samara, PhD; Pashtoon M. Kasi, MD; Robert R. McWilliams, MD; Gloria M. Petersen, PhD; Fergus J. Couch, PhD

- Case-control analysis
- 3030 PC patients, 10/12/2000 to 3/31/2016
- 21 gene panel (DNA repair; cancer) sequenced
- Reference public controls with exome sequence data:
  - 123,136 in the Genome Aggregation Database
  - 53,105 in the Exome Aggregation Consortium database

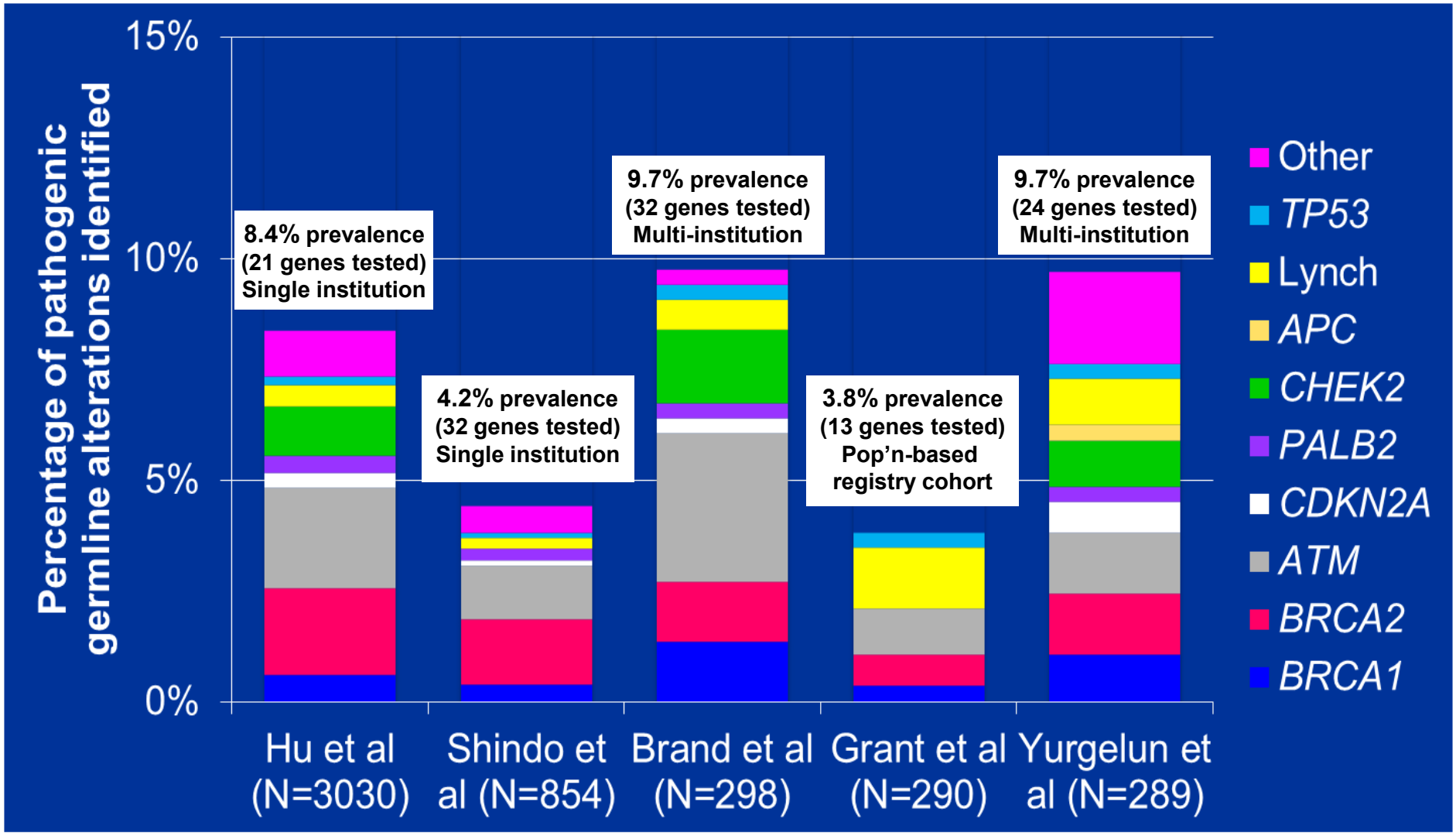
Prevalence of germline mutations in over 3,000 unselected pancreatic cancer patients at Mayo Clinic, 2000-2016

	Cases			Cancer risk			
Gene	Cases with Mutations	Individuals Tested	%	OR	95% CI lower	95% CI upper	Adjusted p-value
CDKN2A	9	2999	0.33	12.33	5.43	25.61	<.001
TP53	6	2999	0.20	6.70	2.52	14.95	<.001
MLH1	4	2999	0.17	6.66	1.94	17.53	.01
BRCA2	57	2999	1.95	6.20	4.62	8.17	<.001
ATM	69	2999	2.28	5.71	4.38	7.33	<.001
BRCA1	18	2999	0.59	2.58	1.54	4.05	.002
PALB2	12	2999	0.40	2.33	1.23	4.01	.087
CHEK2	33	2999	1.10	1.31	0.91	1.83	>0.99

5.9% of all pancreatic cancer patients carry mutations

8.4% of patients with mutations had a family history of pancreatic cancer

Multi-gene panel testing in Pancreatic Cancer

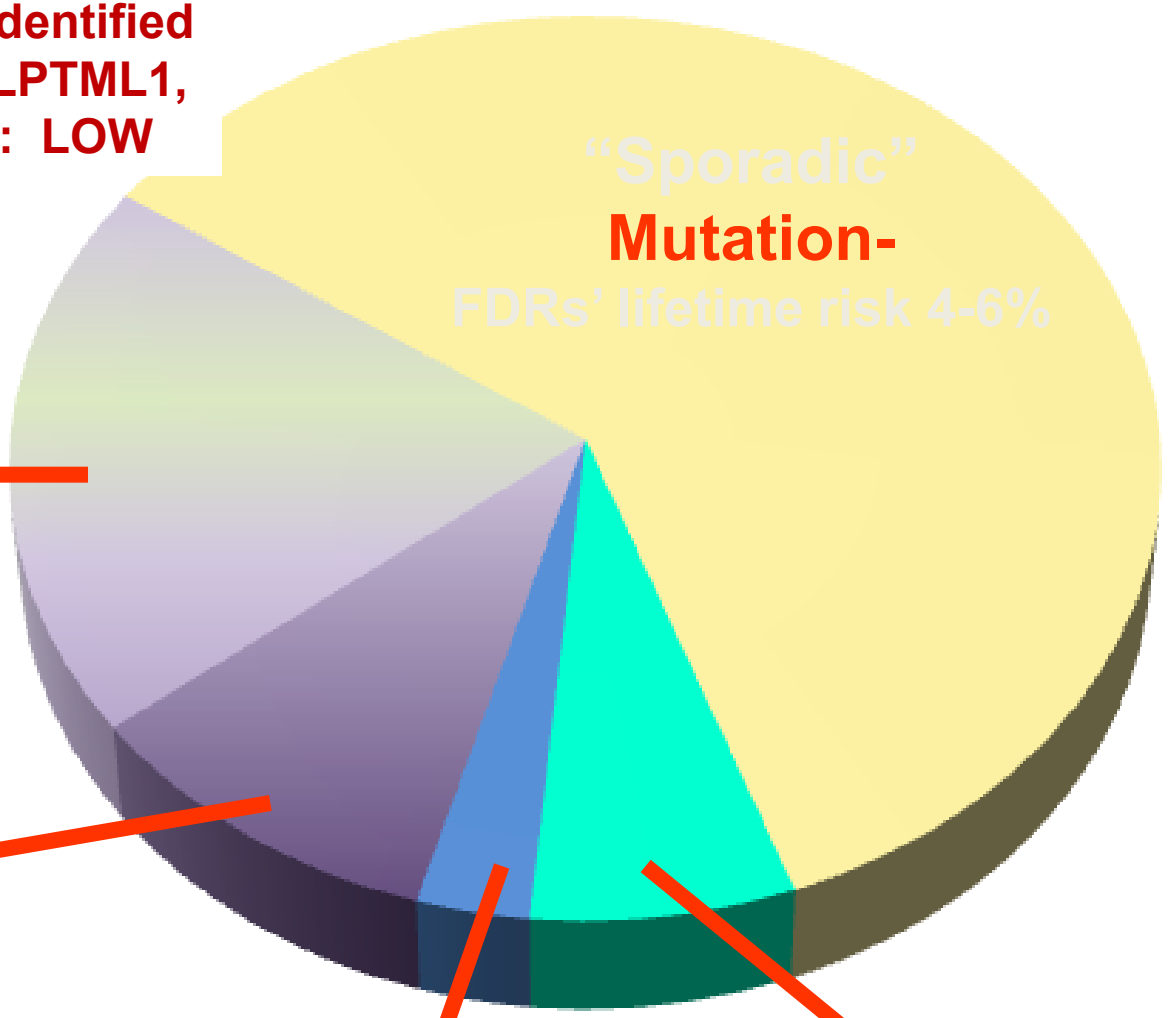


Hu C, et al. *JAMA* 2018;319:2401-9., Shindo K, et al. *J Clin Oncol* 2017;35:3382-90., Brand R, et al. *Cancer* 2018;ePub., Grant RC, et al. *Gastroenterology* 2015;148:556-64., Yurgelun MB, et al. *Genet Med* 2018;ePub.

Courtesy of Matt Yurgelun, MD

Heterogenous genetic factors: Lifetime risk

Genetic polymorphisms identified by GWAS (ABO, TERT, CLPTML1, etc) Carrier lifetime risk: LOW



Young onset, ~20% FDRs' lifetime risk: 6-8%

"Sporadic" Mutation+ FDRs' lifetime risk: 10-30%+

Positive Family History, including uncommon hereditary syndromes; Mutation+ FDRs' lifetime risk: 20-50%

Positive Family History Mutation- FDR's lifetime risk: 8%+

Should All Pancreatic Cancer Patients Be Offered Germline Testing?

EDITORIAL

Germline Genetic Testing for Pancreatic Ductal Adenocarcinoma at Time of Diagnosis

Sapna Syngal, MD, MPH; C. Sloane Furniss, PhD

VOLUME 35 · NUMBER 30 · OCTOBER 20, 2017

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EDITORIAL

Germline Testing for Individuals With Pancreatic Cancer: The Benefits and Challenges to Casting a Wider Net

Matthew B. Yurgelun, *Dana-Farber Cancer Institute; Brigham & Women's Hospital; and Harvard Medical School, Boston, MA*

editorial

Should We Lower Our Threshold for Germline Genetic Assessment in Pancreatic Adenocarcinoma?

See accompanying articles doi:https://doi.org/10.1200/PO.17.00087, https://doi.org/10.1200/PO.17.00098 and https://doi.org/10.1200/PO.17.00152

Syngal S and Furniss CS. *JAMA* 2018;319:2383-5.,Schwark AL and Stadler ZK. *JCO Precis Oncol* 2018;ePub., Yurgelun MB. *J Clin Oncol* 2017;35:3375-7.

Published at jco.org on November 20, 2018. J Clin Oncol 36.

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Evaluating Susceptibility to Pancreatic Cancer: ASCO Provisional Clinical Opinion

Elena M. Stoffel, Shannon E. McKernin, Randall Brand, Marcia Canto, Michael Goggins, Cassadie Moravek, Arun Nagarajan, Gloria M. Petersen, Diane M. Simeone, Matthew Yurgelun, and Alok A. Khorana

Provisional Clinical Opinion

All patients diagnosed with pancreatic adeno… risk for hereditary syndromes k… enocarci-noma. … cancer. Individu… criteria for fami… history of pancr… creatic cancer i… romes associate… er and are candi… susceptibility may be dis-cussed w… cancer, even if family history is unremarkable. Benefits a… creatic cancer screening should be discussed with individuals whose family history meets criteria for FPC and/or genetic susceptibility to pancreatic cancer.

Germline genetic testing for cancer susceptibility may be discussed with individuals diagnosed with pancreatic cancer, even if family history is unremarkable.

NCCN Guidelines Version 2.2019
Pancreatic Adenocarcinoma

CLINICAL PRESENTATION → **WORKUP**

Clinical suspicion of pancreatic cancer or evidence of dilated pancreatic and/or bile duct (stricture)

→ **Pancreatic protocol CT (abdomen)** (See PANC-A)

→ **Multidisciplinary consultation**[a]

No metastatic disease

- Chest and pelvic CT[c]
- Consider endoscopic ultrasonography (EUS)[b]
- Consider MRI as clinically indicated for indeterminate liver lesions
- Consider PET/CT in high-risk patients[d]
- Consider ERCP with stent placement[e]
- Liver function test and baseline CA 19-9 after adequate biliary drainage

Germline testing if diagnosis confirmed[f]

→ **No mass or diagnosis not confirmed** → **Refer to high-volume center for evaluation**

→ Resectable Disease (see PANC-2)

→ Borderline Resectable Disease (see PANC-3)

→ Locally Advanced Disease (see PANC-6)

→ Metastatic Disease (see PANC-8)

Metastatic disease → **Biopsy confirmation, from a metastatic site preferred** →

- **Germline testing**[f]
- **Gene profiling of tumor tissue as clinically indicated**[g]

→ Metastatic Disease (see PANC-8)

[a]Multidisciplinary review should ideally involve expertise from diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, pathology, geriatric medicine, and palliative care. Consider consultation with a registered dietitian. See NCCN Guidelines for Older Adult Oncology and NCCN Guidelines for Palliative Care.

[b]EUS to confirm primary site of involvement; EUS-guided biopsy if clinically indicated.

[c]Imaging with contrast unless contraindicated.

[d]PET/CT scan may be considered after formal pancreatic CT protocol in high-risk patients to detect extra pancreatic metastases. It is not a substitute for high-quality, contrast-enhanced CT. See Principles of Diagnosis, Imaging, and Staging (PANC-A).

[e]See Principles of Stent Management (PANC-B).

[f]Germline testing is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes. Genetic counseling is recommended for patients who test positive for a pathogenic mutation or for patients with a positive family history of cancer, especially pancreatic cancer, regardless of mutation status. Okur V, Chung WK. The impact of hereditary cancer gene panels on clinical care and lessons learned. *Cold Spring Harb Mol Case Stud*. 2017;3(6):a002154. See Discussion and see NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast and Ovarian.

[g]Tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon but actionable mutations. Testing on tumor tissue is preferred; however, cell-free DNA testing can be considered if tumor tissue testing is not feasible. See Discussion.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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NCCN Guidelines Version 2.2019
Pancreatic Adenocarcinoma

NCCN Guidelines Index
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Discussion

CLINICAL PRESENTATION **WORKUP**

Clinical suspicion of pancreatic cancer or evid… of d… pan… and/… bile … (stri…

Pancreatic …

No metastatic disease

- **Chest and pelvic CT[c]**
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- **Consider PET/CT in high-risk patients[d]**
- **Consider ERCP with stent placement[e]**
- **Liver function test and …**

No mass or diagnosis not confirmed → **Refer to high-volume center for evaluation**

Resectable Disease (see PANC-2)

Borderline Resectable Disease (see PANC-3)

…NC-8)

…Disease …8)

[a]Multi… imag… surge… cons… Onco…

[b]EUS … indica…

[c]Imagi…

[d]PET/C… risk pa… high-quality, contrast-enhanced CT. See Principles of Diagnosis, Imaging, and Staging (PANC-A).

[e]See Principles of Stent Management (PANC-B).

…etic …c …impact …(d… …NCCN …Breast and Ovarian.

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Management of patients with increased risk for familial pancreatic cancer (Updated CAPS Consortium). Goggins et al. Gut. 2019 Oct 31.

- Consensus was reached on 55 statements.
- Main goals of surveillance are to identify high-grade dysplastic precursor lesions and T1N0M0 pancreatic cancer
- For those with familial risk, surveillance should start no earlier than age 50 or 10 years earlier than the youngest relative with pancreatic cancer, but start at age 50 or 55 (not full consensus).
- Preferred surveillance tests are EUS and MRI/MRCP performed in a research setting by multidisciplinary teams with appropriate expertise

Collaborators & Acknowledgments

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