PANCREATIC CANCER ACTION NETWORK®

GENETICS OF PANCREATIC CANCER

August 10, 2020

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JOHNS HOPKINS MEDICINE

Genetics of Pancreatic Cancer

Alison Klein, PhD MHS
Professor of Oncology, Pathology and Epidemiology
Johns Hopkins Medicine

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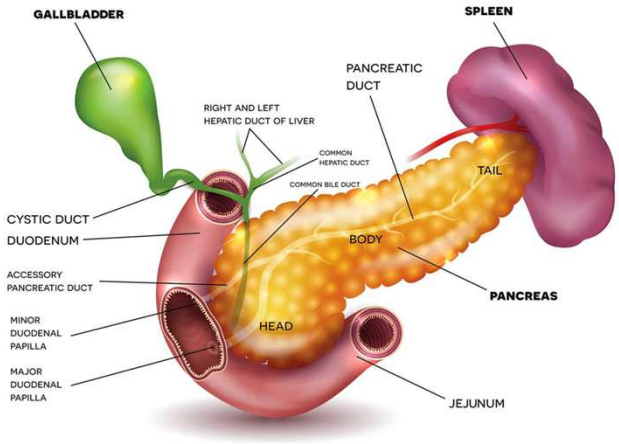
The Pancreas



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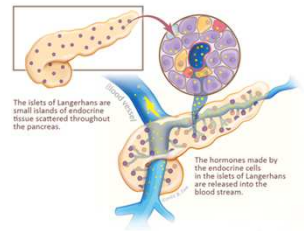
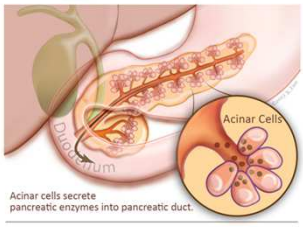
Function of Pancreas





	Acinar cells are the exocrine (exo=outward) cells of the pancreas that produce and transport enzymes that are passed into the duodenum where they assist in the digestion of food.
Islets of Langerhans	The islets of Langerhans are the endocrine (endo= within) cells of the pancreas that produce and secrete hormones such as insulin and glucagon into the bloodstream. The pancreatic hormones, insulin and glucagon, work together to maintain the proper level of sugar (glucose) in the blood. Blood sugar is used by the body for energy.

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Global Trends

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Global Trends

JOHNS HOPKINS MEDICINE

- The global burden of pancreatic cancer more than doubled from 1990 to 2017
  - 195 000 cases in 1990
  - 448 000 cases in 2017

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Global Trends

- Increase due to
  - Advancing age of the population
  - 2012 8% population >65
  - 2015 8.5% population > 65
  - By 2050 >16.7% population >65
- Improved diagnosis
- Increase in age adjusted rates
  - Increasing obesity
    - prevalence tripled since 1975
    - Rates of alcohol and diabetes have doubled
    - Smoking decreased in some regions, remains high in Asia

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Pancreatic Cancer in USA

- In 2020, there will be
  - 57,600 incident pancreatic cancers
  - 47,050 deaths due to pancreatic cancer
- 3nd leading cause of cancer death
- >90% of pancreatic neoplasm are PDAC
- 5 year survival – 10%
  - 20% of patients present with “resectable disease”
    - 5 year survival ~40%

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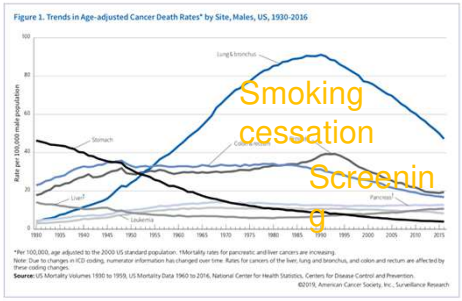
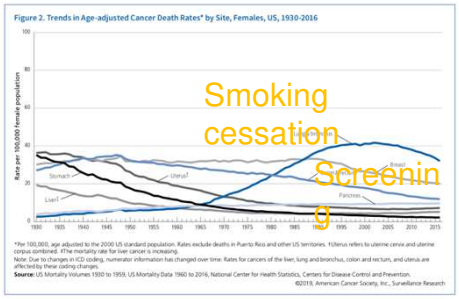
3rd leading cause of Cancer Death
57,600 new diagnoses projected in 2020





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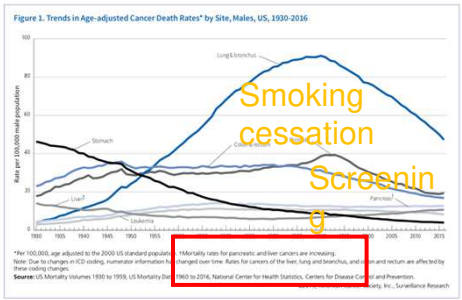
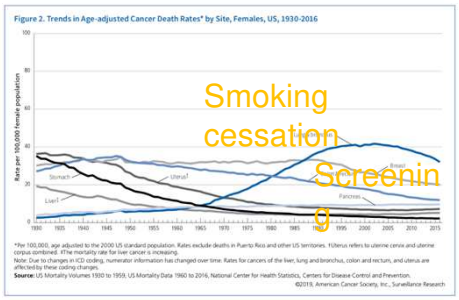
3rd leading cause of Cancer Death
57,600 new diagnoses projected in 2020





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3rd leading cause of Cancer Death
57,600 new diagnoses projected in 2020

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Precursors

- IPMN: intraductal papilloary mucinous neoplasm
  - Macroscopic
  - 7+ decade
  - Can occur in branch or main duct (branch duct IPMNs may be more aggressive
- MCN: mucinous cystic neoplasm
  - Macroscopic
  - Occur in body and tail
  - More common in women
  - 5th decade of life
- PanIN: pancreatic intraeplithial neoplasia
  - Most common precursors to PDA
  - microscopic

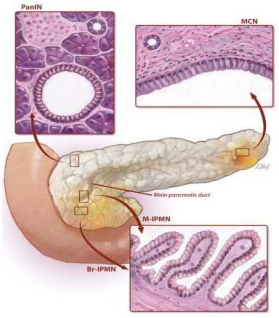

Figure 1. Distinct precursors to invasive ductal adenocarcinomas of the pancreas. Preinvasive lesions in the ductal epithelium differ in size, location, histologic appearance, and clinical behavior. IPMN, intraductal papillary mucinous neoplasm (M-, main duct; Br-, branch duct); MCN, mucinous cystic neoplasm; PanIN, pancreatic intraepithelial neoplasia. Artwork by David W. Ehlert.

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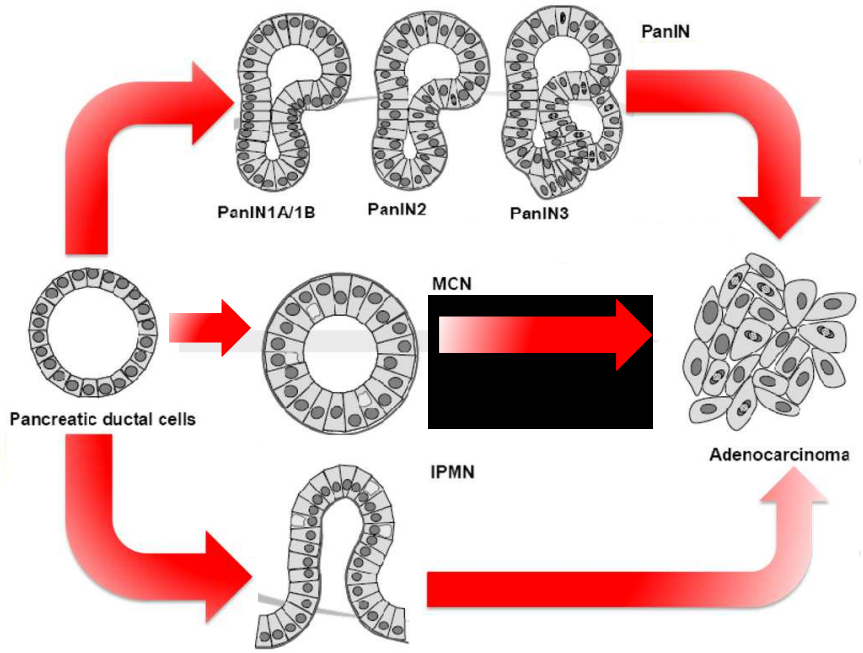

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Pancreatic Cancer Risk Factors	
Cigarette Smoking	2-fold in current smokers
Obesity	1.3 fold in highest BMI categories
Heavy Alcohol Use	1.6 fold in heavy drinkers (>6-10 per day)
New Onset Diabetes	0.8% develop PDAC in 3 years
Long-Standing Diabetes	Up to 2 fold in individuals with diabetes >10 years
Family History	2 fold – 1 family member 7 fold – >1 family member
Pancreatic Cysts	3-10% progress to PDAC within 10 years
Pancreatitis	2-3 fold for chronic pancreatitis

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Challenges to Detection & Screening

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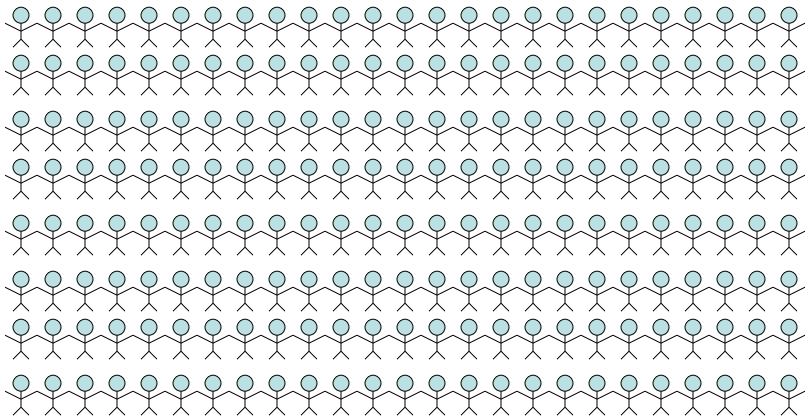
The Challenges: PDAC is Rare



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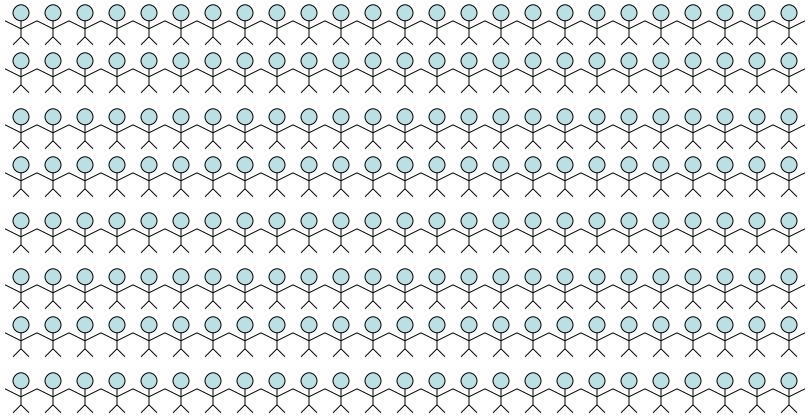
200 US Whites age 65



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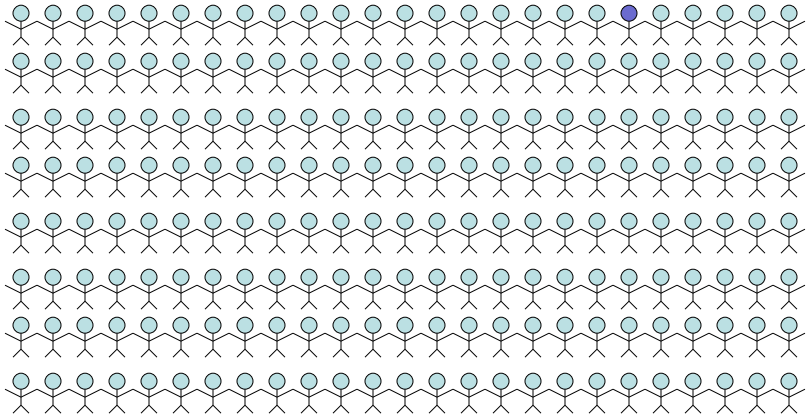
10 years later: 1 PDAC



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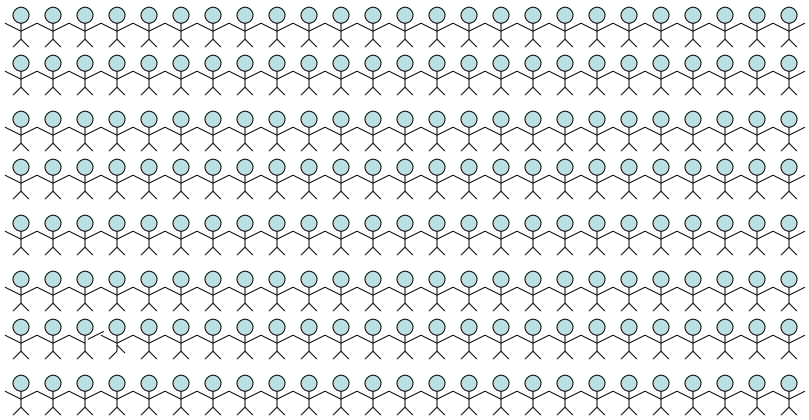
200 Current Smokers US White age 65



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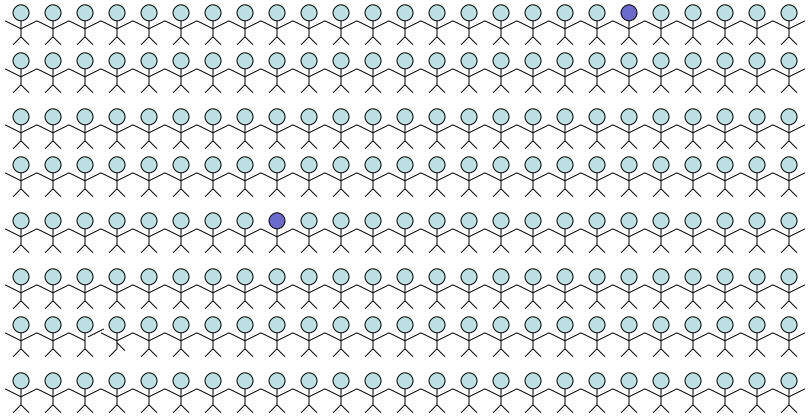
Current Smokers 10 years later: 2 PDAC



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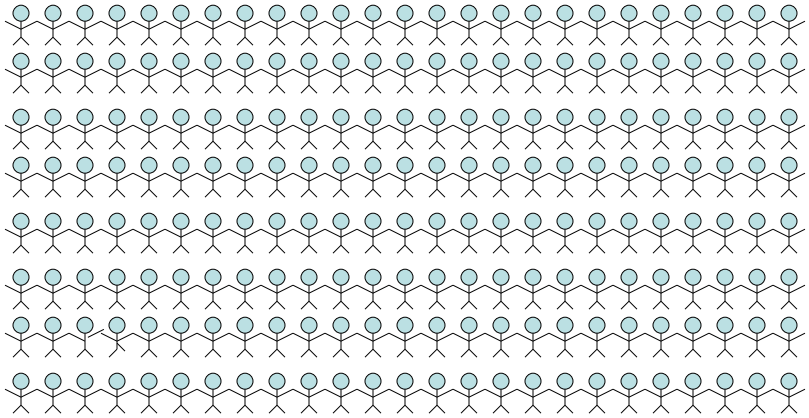
Why modeling Breast Cancer is simpler



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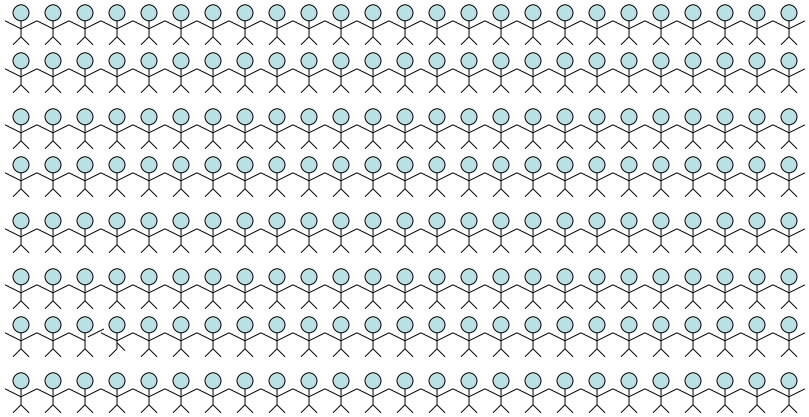
200 US White Women age 65



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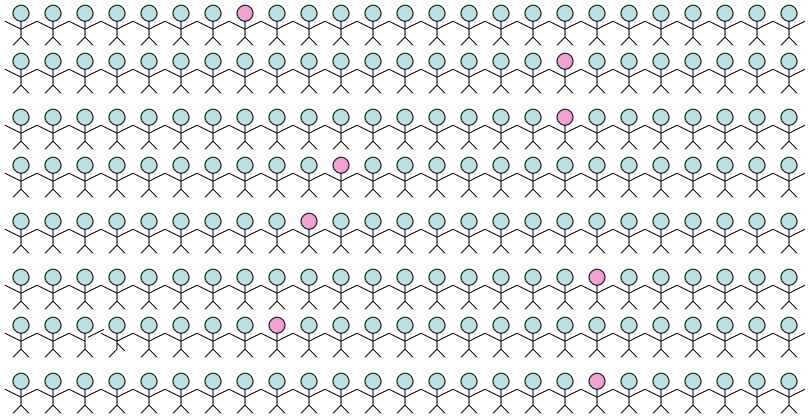
10 years later
8 Breast Cancers



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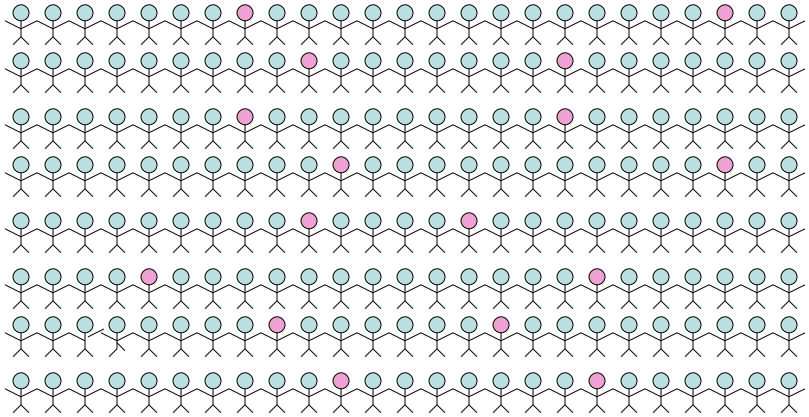
10 years later: 2 fold Risk Factor
16 Breast Cancers



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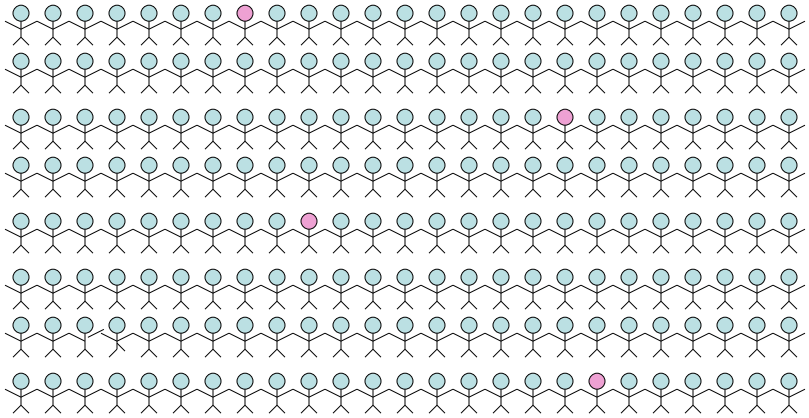
10 years later: ½ fold Risk Factor
4 Breast Cancers



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Pancreatic Cancer Genetics

Identification of pancreatic cancer susceptibility genes can aid in the early detection and lead to targeted therapy for pancreatic cancer.

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Familial Pancreatic Cancer

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- Family history of pancreatic cancer strongly associated with increased risk
  - OR >2 for one affected relative
- Familial Pancreatic Cancer
  - Pair of first degree relatives in kindred with PC
  - 7 X risk of general population
  - Risk increased with increasing FH

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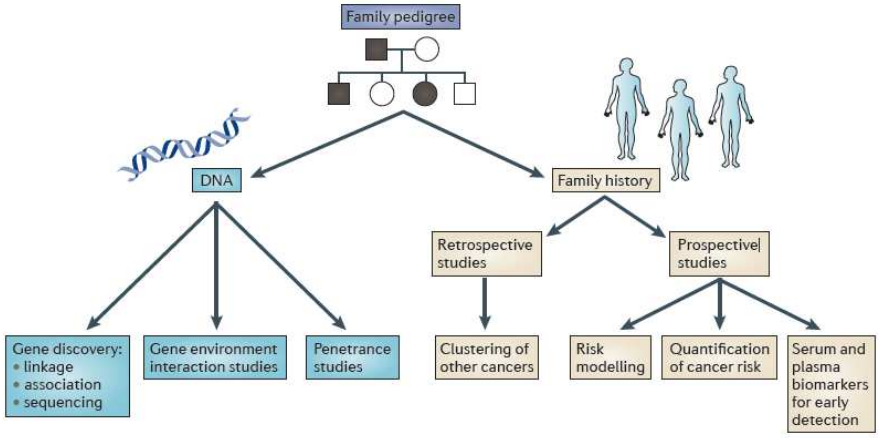

Figure 1 | **Overview of the research conducted with pancreatic cancer family registry data.** Family registries represent a collection of data that typically includes a detailed family history, as well as blood or saliva for DNA studies. This information can be used in a variety of research studies, including gene discovery and cancer risk. The family data can be expanded to capture pathology samples and prospective data collection that enable other studies, such as prospective studies and biomarker studies, to be carried out.

Klein Nature Cancer Reviews 2013

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National Familial Pancreas Tumor Registry (NFPTR)

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- 7,539 Families enrolled (9/13/2019):
  - 5,417 Non-Familial Kindreds
  - 2,122 Familial Kindreds (>= 2 FDR with PC)

Number of Affected	Number of Kindreds
2	1352
3	521
4	182
5 or more	92

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National Familial Pancreas Tumor Registry (NFPTR)

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- 309 incident cancers
  - –287 in relatives
  - –22 in spouses

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PDAC Risk from Family History

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- **One close relative**
  - **2.14-fold (0.58-5.49)**
- ***Familial Pancreatic Cancer (2 FDR)***
  - **6.79 fold (95% CI 4.94-5.75) overall**
  - **17.02 fold (95%CI 7.34-33.5) 3+ close relatives**
- **Age of Onset in kindreds predicts future risk in FPC kindreds but not SPC**

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Excess Risk of Extra-pancreatic cancers

	Family History		Youngest Age of Onset	
	Sporadic	**Familial**	**<50**	**>= 50**
Extrapancreatic cancers	**1.55 (1.39-1.73)**	**1.41 (1.26-1.58)**	**1.52 (1.23-1.85)**	**1.47 (1.35-1.61)**
Breast	1.06 (0.66-1.62)	**1.66 (1.15-2.34)**	**1.98 (1.01-3.52)**	1.26 (0.91-1.71)
Ovarian	1.28 (0.58-2.48)	**2.05 (1.10-3.49)**	2.75 (0.88-6.52)	1.50 (0.87-2.4)
Colon	1.19 (0.81-1.70)	1.33 (0.93-2.86)	**2.31 (1.30-3.81)**	1.13 (0.84-1.5)
Bile Duct	**3.01 (1.09-6.67)**	**2.89 (1.04-6.39)**	1.93 (0.05-1.09)	**3.10 (1.52-5.64)**
Prostate	1.29 (0.80-1.97)	1.19 (0.73-1.83)	**2.31 (1.14-4.20)**	1.08 (0.73-1.53)

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Why Family History and/or mutation status use for PDAC risk modeling

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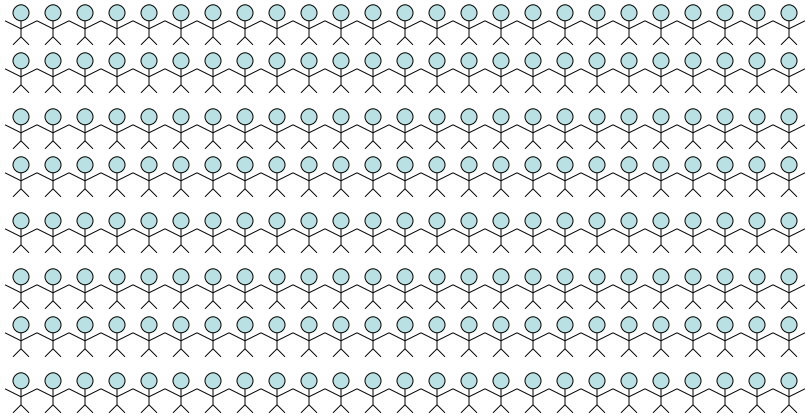
200 US Whites age 65
> 1 Familial PDAC Member



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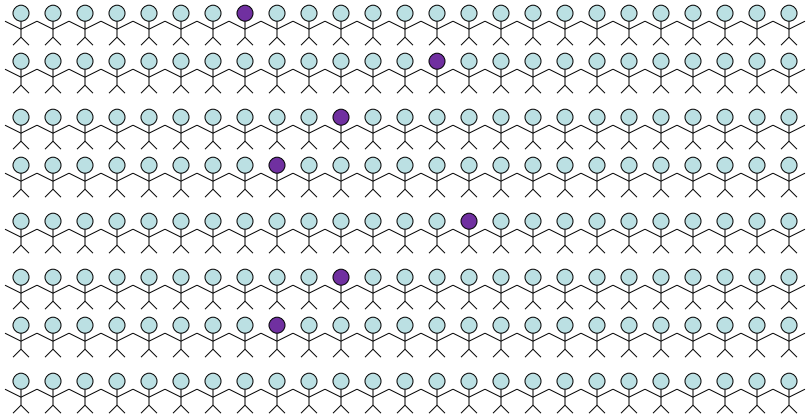
10 years later
> 1 Familial PDAC Member



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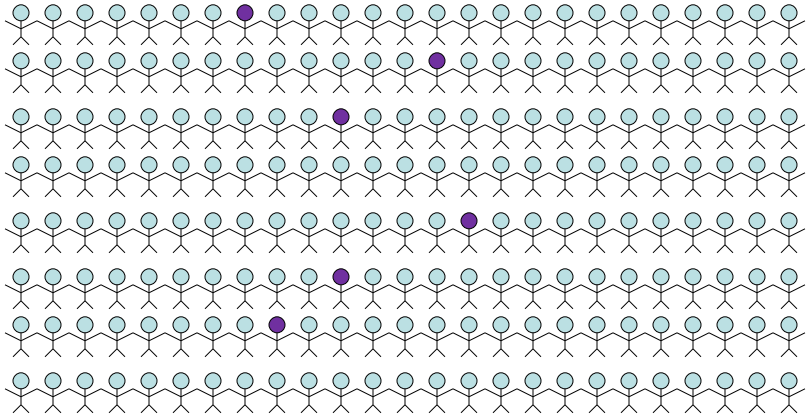
10 years later
> BRCA2 mutation carrier



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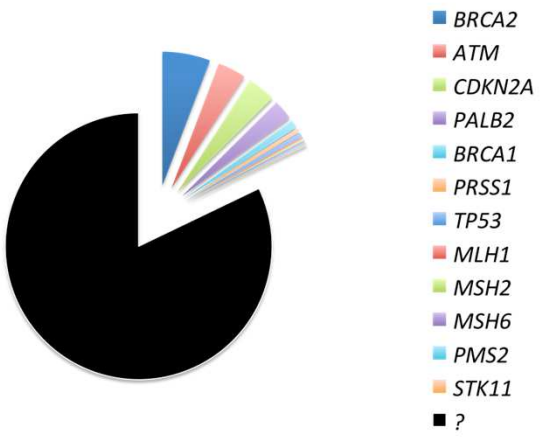
Proportion of FPC attributed to known mutations



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Slide courtesy of N. Roberts

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BRCA2 and Pancreatic Cancer

- Of the known genetic causes of FPC *BRCA2* mutations account for the largest portion of families.
- ~17% of patients with 3 relatives with pancreatic cancer have a germline *BRCA2* mutations Cancer Research 2002:56:5360
- ~12% of patients with 2 relatives with pancreatic cancer have a germline *BRCA2* mutations JNCI 2003;95:214-21
- ~6% of patients with from moderate risk PC families have deleterious *BRCA2* mutations Couch et al CEBP 2007

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Association not limited to patients with a Family History

- ~5-7% of patients with "sporadic" pancreatic cancer have germline *BRCA2* mutations Goggins et al Cancer Research 1997, Holder et al 2015
- 4.1% of AJ PC patients harbor 6174delT Ferrone JCO 2008
- BRCA2 Carriers have a 3.5-6+ fold increased risk of PC

SIR= 5.79 (95%CI 4.28-7.84) BCFR Mocci et at CEBP 2013

RR = 3.51; 95% CI = 1. 87-6.58 BCLC JNCI 1999

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BRCA1 and Pancreatic Cancer

- **BRCA1 carriers have a 1 - 4 fold increased risk of pancreatic cancer**
- ~0/66 patients from FPC kindreds carried deleterious *BRCA1* mutations. Cancer Biology and Therapy 2009:131-135
- ~1.3% unselected Jewish PC patients had deleterious BRCA1 mutations Ferrone JCO 2008
  - SIR = 4.11 (95%CI 2.94-5.76) BCFR Mocci et at CEBP 2013
  - RR = 2.25 (95% CI 1.26- 4.06) Thomson JNCI 2002
  - RR = 3.1 (95% CI 0.45–21) Risch JNCI 2006
- Lifetime Risk 3.6% (95% CI = 1.9% to 5.3%) Brose et al JNCI 2002

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Familial Melanoma

- Familial Melanoma can be caused by germline mutations in the *CDKN2A* gene NEJM 1995; 333:970
- Pancreatic Cancer 2nd most common cause of cancer death in these families
- 9-38 Fold increased risk of developing pancreatic cancer

  Int J Cancer 2000; 809-811
  Cancer 2003;798-804
- 17% lifetime risk of developing pancreatic cancer

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Lynch Syndrome

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- Results from germline mutations in *MLH1*, *MSH2*, *MSH6*, *PMS2* resulting in a deficient DNA mismatch repair system
- Some studies report an increased risk of PC HNPCC, up to SIR 8.6 (95% CI, 4.7–15.7)

Kastrinos et al 2009

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Hereditary Pancreatitis

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- Hereditary pancreatitis is characterized by the autosomal dominant inheritance of severe episodes of pancreatitis beginning at a young age
- Caused by germline mutations in *PRSS1*

Nature Genetics 1996; 14:141

- 40% of patients with hereditary pancreatitis will develop pancreatic cancer in their lifetime

Lowenfels JNCI 1997

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PALB2

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- Of 5 FPC patients sequenced 1 had a germline truncating variant as well as a somatic mutation in the *PALB2* gene
- 3 of 96 Additional FPC patients sequenced also had truncating *PALB2* mutations Jones et al Science 2009
- Subsequent studies have replicated this finding
  - Tischkowitz et al examined 101 FPC patients
  - A single PALB2 deletion was reported in a patient with familial pancreatic cancer, patient also a prior history of breast cancer

ATM

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- Germline mutations identified in WES & WGS of FPC kindreds
- 2/38 kindreds had deleterious ATM shared among relatives with PC
- Analysis of 166 additional FPC kindreds identified four variants deleterious identified (0 in the controls (P=0.04))

  Roberts et al Cancer Discovery 2011
- Subsequent studies have replicated the association

  Roberts et al Cancer Discovery 2015

GERMLINE TESTING FOR ALL PANCREATIC CANCER PATIENTS?

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Germline Mutations in Unselected Pancreatic Cancer

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- 1998: 7% JHU surgical patients had BRCA2 mutation (Goggins et al Can Res)
- 2015: 4.6% Toronto surgical patients BRCA1/2 (Holder et al JCO)
- 2017: 3.9% JHU patients multi-gene panel test (Shindo et al JCO)
- 2018: 5.5% Mayo patients multi-gene panel test (Hu et al JAMA)

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Risk Estimates

Gene	OR	Mutation Prevalence in PDAC patients
CDKN2A	12.3 (5.4-25.6)	0,3%
TP53	6.7 (2.5-14.9)	0.2%
MLH1	6.6 (1.9-17.5)	0.13%
BRCA2	6.2 (4.6-8.2)	1.9%
ATM	5.7 (4.4-7.3)	2.3%
BRCA1	2.6 (1.4-4.0)	0.6%
PALB2		0.5%
ALL Mismatch		0.5%

Hu et al JAMA 2018

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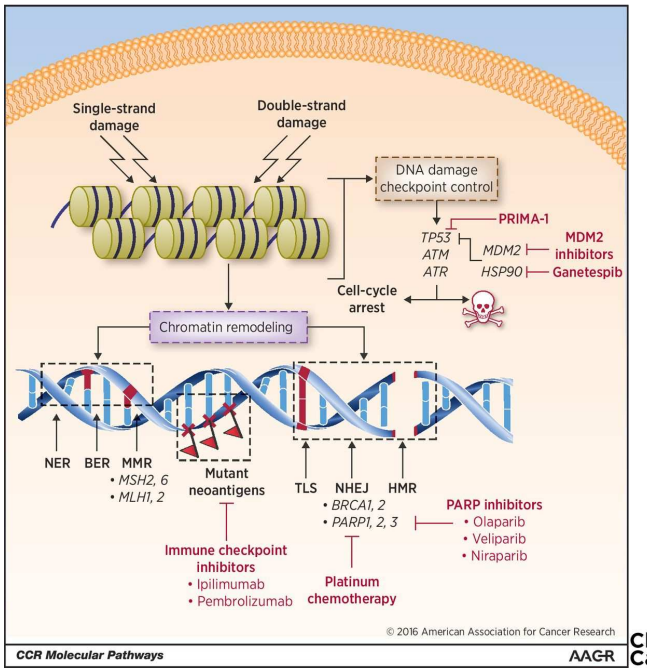

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Niall M. Corcoran et al. Clin Cancer Res 2016;22:3132-3137

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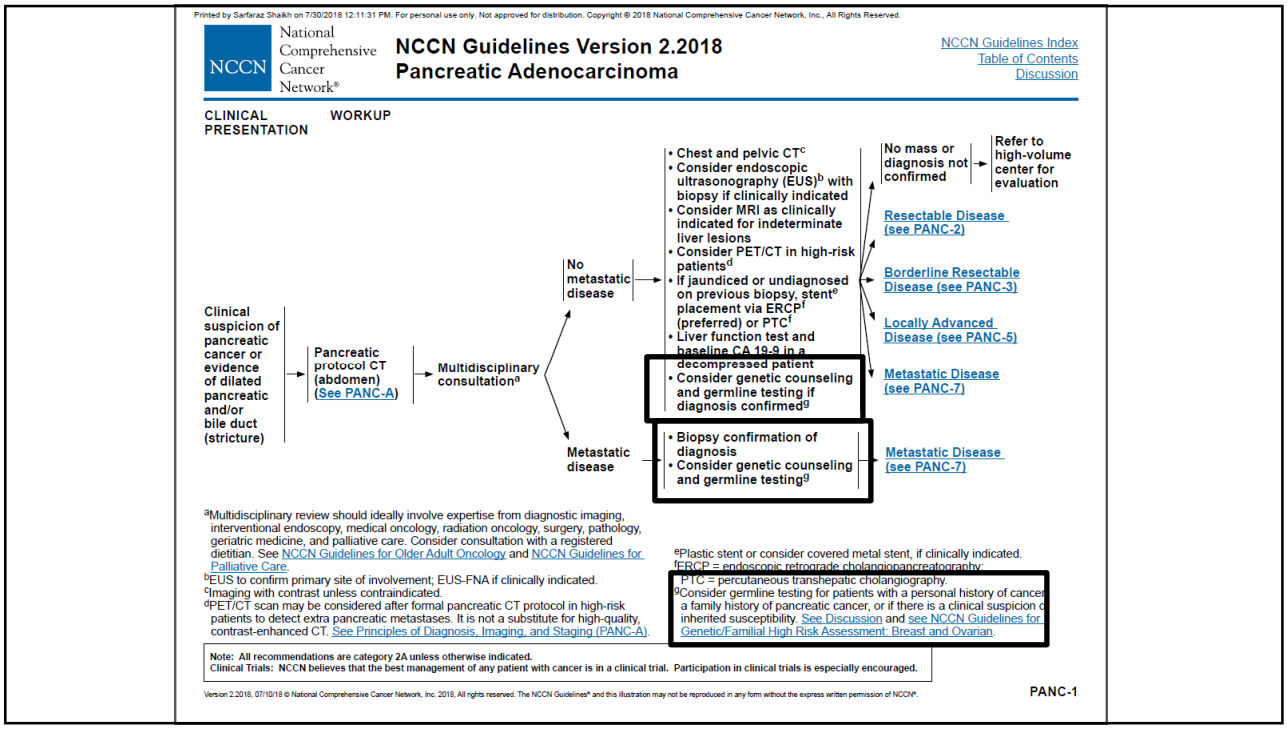

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GENERATE STUDY

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- **GOAL**: To address barriers to genetic testing, the GENERATE Study proposes alternative methods of providing genetic education and testing
- Individual with:
  - A first-degree relative with a diagnosis of pancreatic ductal adenocarcinoma (PDAC)

    OR
  - A second-degree relative with a diagnosis of PDAC who has a known germline mutation in the family in one of these genes: *APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11,* or *TP53*
- United States mailing address & Access to a healthcare provider and willing to share genetic test results with provider/study team
- www. generatestudy.org

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Majority of FPC kindreds still unexplained

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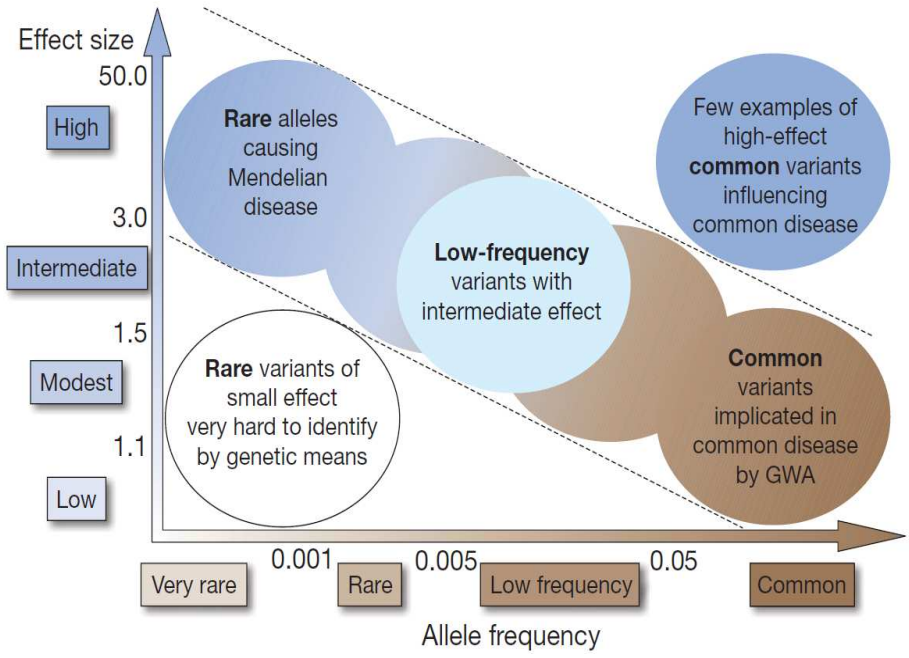

Adapted from Manolio et al 2010, Klein Nat Can Reviews 2012, Childs et al 2016

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JOHNS HOPKINS MEDICINE

High Risk Genes

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RESEARCH BRIEF

Whole Genome Sequencing Defines the Genetic Heterogeneity of Familial Pancreatic Cancer

Nicholas J. Roberts[1,2], Alexis L. Norris[1], Gloria M. Petersen[3], Melissa L. Bondy[4], Randall Brand[5], Steven Gallinger[6], Robert C. Kurtz[7], Sara H. Olson[8], Anil K. Rustgi[9], Ann G. Schwartz[10], Elena Stoffel[11], Sapna Syngal[12], George Zogopoulos[13,14], Syed Z. Ali[1], Jennifer Axilbund[1], Kari G. Chaffee[3], Yun-Chirig Chen[15], Michele L. Cote[10], Erica J. Childs[16], Christopher Douville[15], Fernando S. Goes[17], Joseph M. Herman[18], Christine Iacobuzio-Donahue[19], Melissa Kramer[20], Alvin Makohon-Moore[1], Richard W. McCombie[20], K. Wyatt McMahon[2], Noushin Niknafs[15], Jennifer Parla[20,21], Mehdi Pirooznia[17], James B. Potash[22], Andrew D. Rhim[9,23], Alyssa L. Smith[13,14], Yuxuan Wang[2], Christopher L. Wolfgang[24], Laura D. Wood[1,18], Peter P. Zandi[17], Michael Goggins[1,18,25], Rachel Karchin[15], James R. Eshleman[1,18], Nickolas Papadopoulos[2], Kenneth W. Kinzler[2], Bert Vogelstein[2], Ralph H. Hruban[1,18], and Alison P. Klein[1,16,18]

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FPC patient demographics

Table 1. Characteristics of the whole genome sequenced patients with FPC

Classification	Number
Cohort	
FPC patients	638
FPC kindred	593
Age, y	
Less than 50	35
50-59	124
60-69	214
70-79	185
80+	73
Unknown	7
Genetic ancestry	
African	18
Asian	8
Caucasian	612
Affected relatives	
2	358
3	196
4 or more	84
DNA origin	
Blood	454
Lymphoblastoid cell line	158
Tissue	26

- Whole genome sequencing of germline DNA
- Variants
  - Approx. 4,000,000 changes per pancreatic cancer patient

Roberts *et al.* 2016

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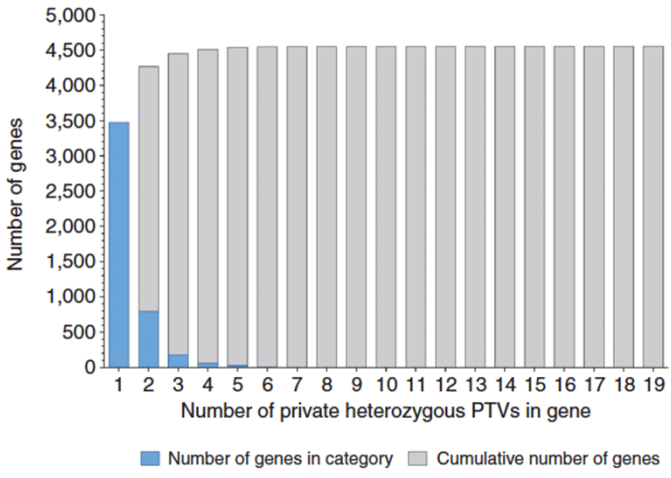
Most genes do not have rare TVs



Roberts *et al.* 2016

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Deleterious variants in FPC patients

- 58 FPC kindreds have deleterious variant in established FPC susceptibility genes (9.8%; 95% CI: 7.6 – 12.4%)
- *ATM* - 20 FPC kindreds (3.4%; 95% CI: 2.2 - 5.2%)
- 4 FPC patients harbor multiple deleterious variants

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Conclusions

- Familial Pancreatic Cancer is highly heterogeneous
- Cause of most familial pancreatic cancer remains unclear
- Interpretation of causative variation is challenging
  - Rare variants
  - Somatic events

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Finding Common Variants associated with Pancreatic Cancer

Genome Wide Association Studies

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Genome-wide Association Studies

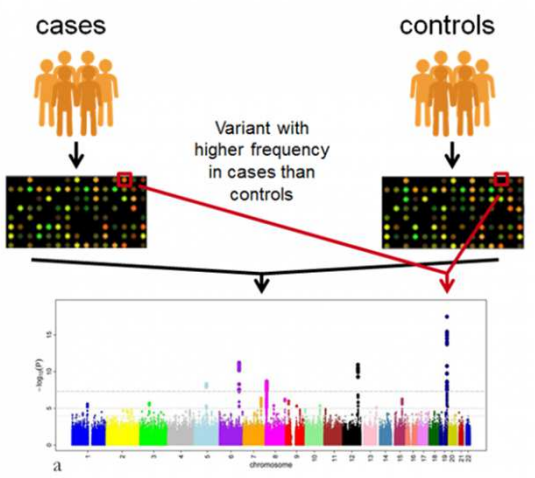

Image From: https://www.ebi.ac.uk/training-beta/online/courses/gwas-catalogue-exploring-snp-trait-associations/what-is-gwas-catalog/what-are-genome-wide-association-studies-gwas/

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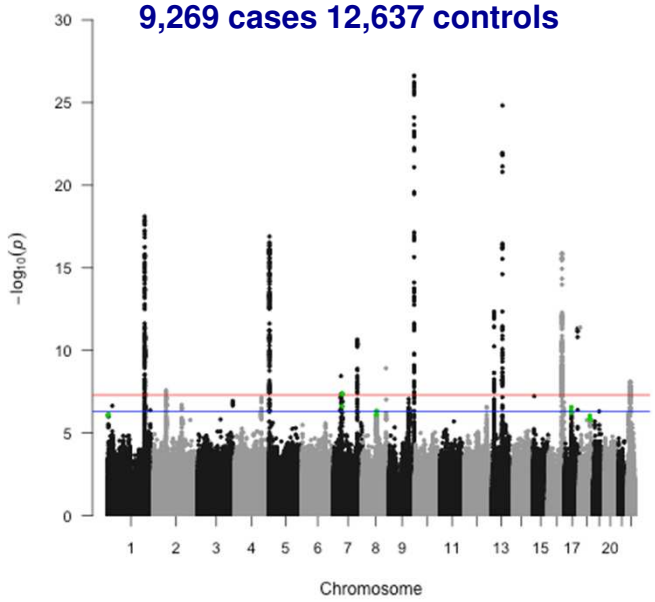
Pancreatic GWAS consortium: Pancreatic Cohort Consortium and Pancreatic Case Control Consortium

9,269 cases 12,637 controls



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Loci Associated with PC Risk

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Chr	Nearby gene	SNP	OR (95% CI)	P-value
1p36.33	*NOC2L*	rs13303010	1.26 (1.19-1.35)	$8.4x10^{-14}$
1q32.1	*NR5A2*	rs3790844	0.81 (0.76-0.86)	$7.6x10^{-16}$
2p14	*ETAA1*	rs1486134	1.14 (1.09-1.19)	$4.6x10^{-9}$
3q28	*TP63*	rs9854771	0.90 (0.86-0.94)	$6.8x10^{-15}$
5p15.33	*CLPTM1L*	rs401681	1.19 (1.15-1.23)	$9.3x10^{-17}$
7p12	*TNS3*	rs73328514	0.71 (0.63-0.80)	$1.7x10^{-8}$
7p14.1	*SUGCT*	rs17688601	0.88 (0.84-0.93)	$1.1x10^{-8}$
7q32.3	*LINC-PINT*	rs6971499	0.79 (0.74-0.84)	$3.0x10^{-12}$
8q21.11	*HNF4G*	rs2941471	0.89 (0.85-0.93)	$6.6x10^{-10}$
8q24.21	*MYC*	rs10094872	1.14 (1.10-1.20)	$1.1x10^{-9}$
9q34.1	*ABO*	rs505922	1.27 (1.22-1.31)	$7.4x10^{-27}$
13q12.2	*PDX1*	rs9581943	1.15 (1.10-1.20)	$5.1x10^{-14}$
13q22.1	*KLF5, KLF12*	rs9543325	1.24 (1.19-1.28)	$1.2x10^{-22}$
16q23.1	*BCAR1*	rs7190458	1.36 (1.27-1.44)	$1.3x10^{-11}$
17q12	*HNF1B*	rs4795218	0.88 (0.84-0.92)	$1.3x10^{-8}$
17q24.3	*LINC00673*	rs11655237	1.25 (1.19 1.30)	$9.5x10^{-15}$
18q21.23	*GRP*	rs1517037	0.86 (0.80-0.91)	$3.3x10^{-8}$
22q12.1	*ZNRF3*	rs16986825	1.21 (1.10-1.20)	$1.2x10^{-8}$

Amundadottir et.al, *Nature Genetics*, 2009
Petersen et.al, *Nature Genetics*, 2010
Wolpin et.al, *Nature Genetics*, 2014
Childs et.al, *Nature Genetics*, 2015
Klein et.al, Nature Communications 2018
Slide adapted from L. Amundadottir

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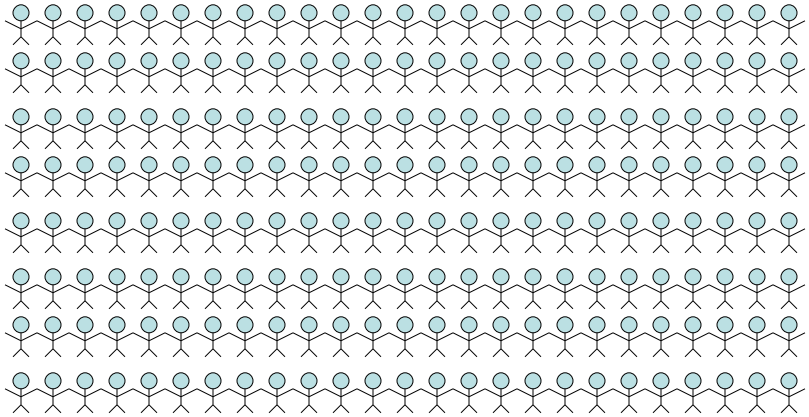
200 US Whites age 65



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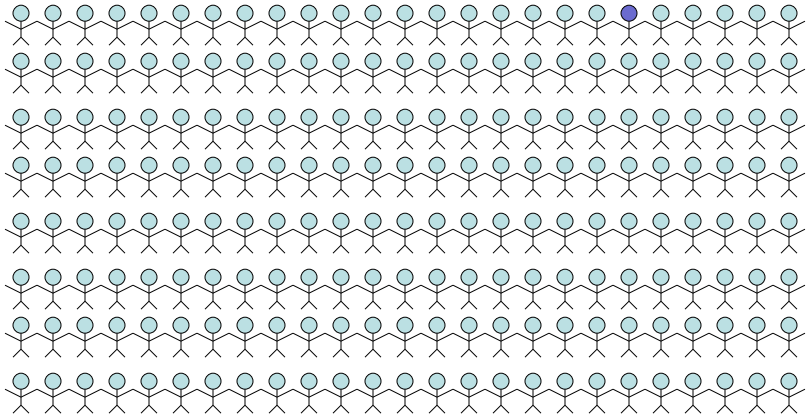
10 years later: 1 PDAC



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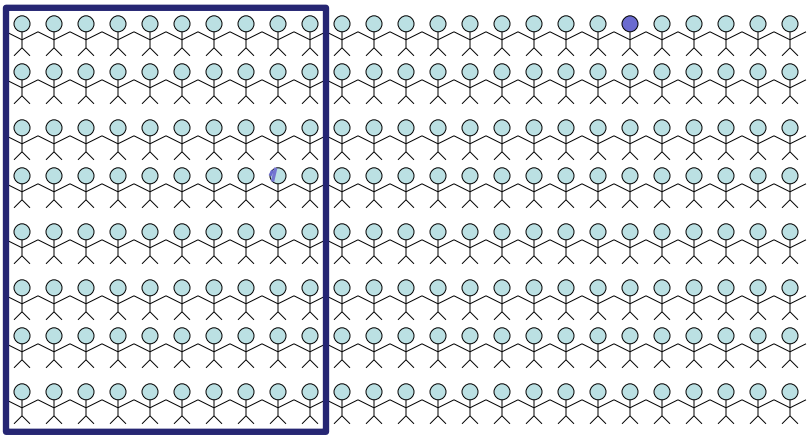
10 years later: 1 PDAC



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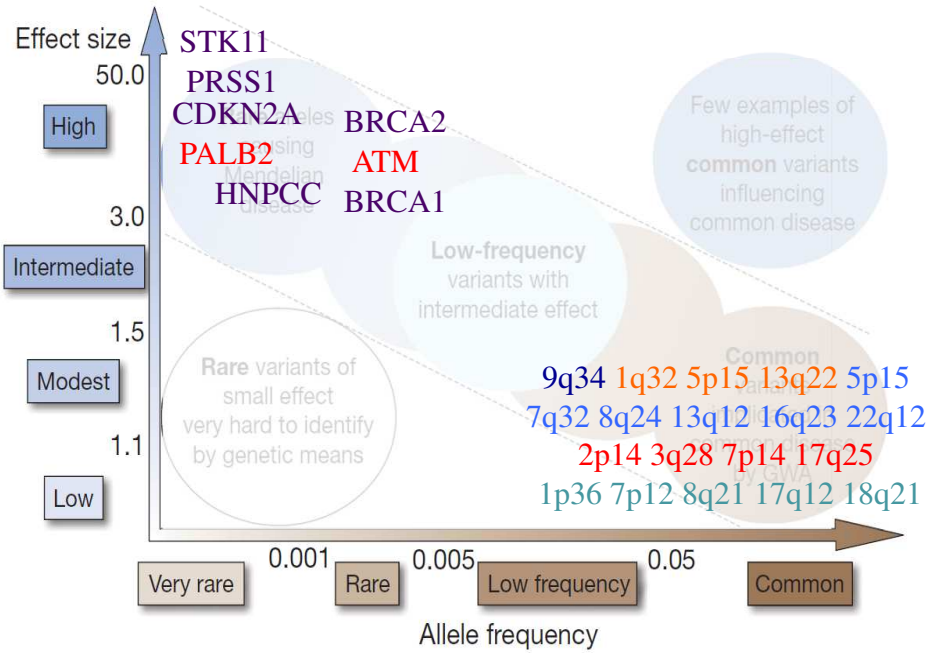

Adapted from Manolio et al 2010, Klein Nat Can Reviews 2012, Childs et al 2016

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Future Studies

- Rare Variants
  - Analysis of the Familial WGS data ongoing
  - WES studies of Unselected pancreatic cancer patients
- Common Variants
  - Secondary Analysis of existing GWAS data
  - Expanding GWAS
    - 10,000 additional Cases- 60,000 Controls

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Genetics of Pancreatic Cancer among individuals of African Ancestry

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African American Pancreatic Cancer Study

- AA have a higher incidence of PC
  - 15.6/100,000 vs 12.3/100,000
- 10% of US PDAC patients are Black
  - 5,866 in 2014 and 3,780 in 2007

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Disparities in outcomes

- Median Age 67 years
- Resection rates for early stage disease are comparable in Blacks and White (Sohn et al Cancer 2010)
- More likely to have locally advanced or metastatic disease
- Median survival 5 months
- Less likely to receive care at NCCN guidelines

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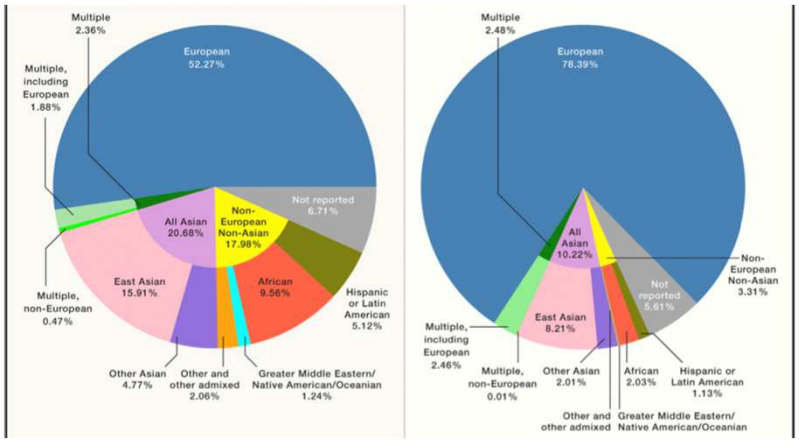
Genetic Studies Lack Representation



From Sirugo et al The Missing Diversity in Genetic Studies Cell 2019

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Improving detection

JAMA Network™

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

JAMA. 2019;322(5):438-444. doi:10.1001/jama.2019.10232

Population	**Asymptomatic adults** (not known to be at high risk of pancreatic cancer)
Recommendation	Grade: D Do not screen.

Risk Assessment	Persons with certain inherited genetic syndromes or a history of familial pancreatic cancer are at high risk of pancreatic cancer. This recommendation does not apply to these high-risk populations. Other factors such as new-onset diabetes, preexisting diabetes, older age, cigarette smoking, obesity, or a history of chronic pancreatitis increase risk to a lesser degree. Asymptomatic persons who have these risk factors are included in this recommendation.
Screening Tests	The USPSTF does not recommend screening for pancreatic cancer in the general population using any method. Imaging-based methods, such as the computed tomography scan, magnetic resonance imaging, and endoscopic ultrasonography, have been studied as screening tests in trials of screening persons at high risk of pancreatic cancer due to inherited genetic syndromes or familial pancreatic cancer. There are currently no accurate, validated biomarkers for early detection of pancreatic cancer.
Treatment and Interventions	Surgery (pancreaticoduodenectomy [known as the Whipple procedure] or total or distal pancreatectomy) is the generally recommended treatment for pancreatic cancer that is deemed to be resectable at the time of diagnosis. Neoadjuvant or adjuvant chemotherapy may be recommended, depending on the stage of cancer and other factors.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to https://www.uspreventiveservicestaskforce.org.

Figure Legend: U.S. Preventive Services TASK FORCE JAMA

Clinical Summary: Screening for Pancreatic Cancer

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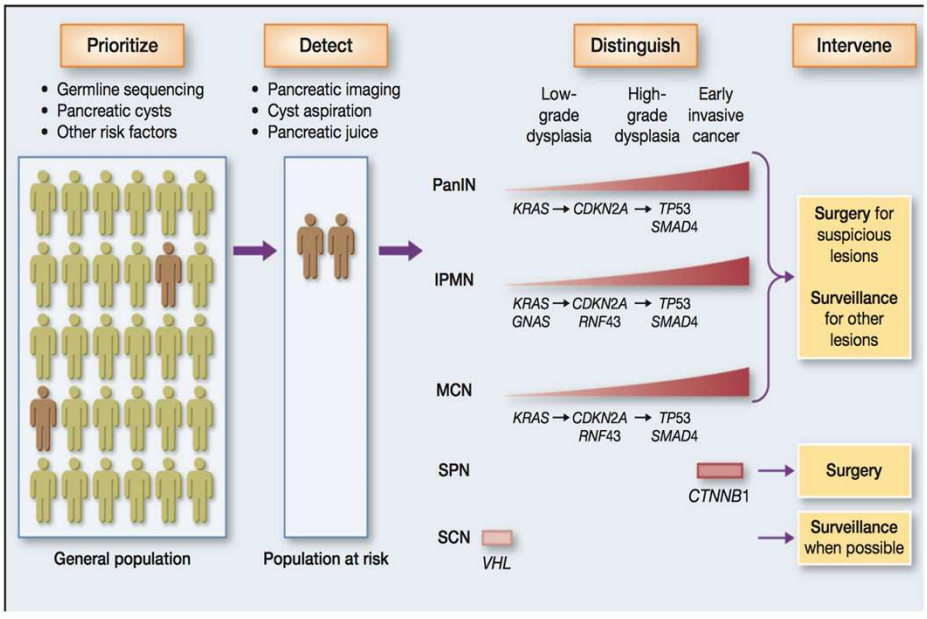

Lennon AM et al. *Cancer Research* 2014

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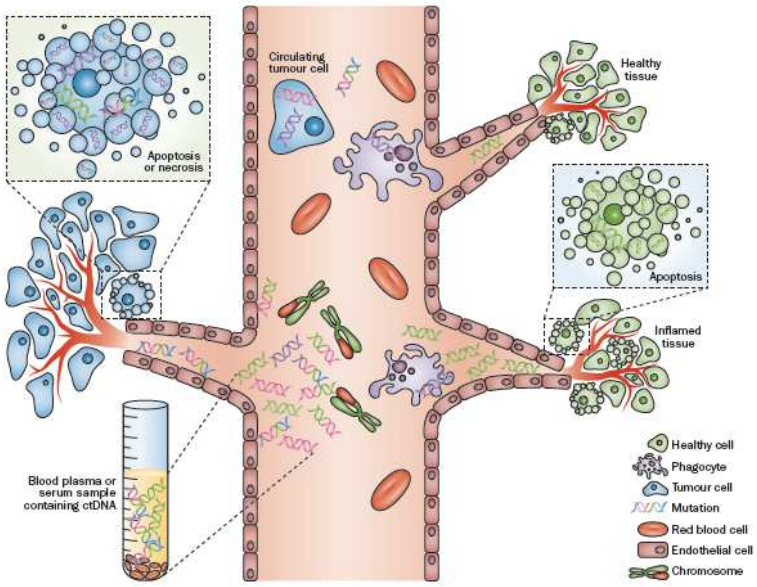

Figure 1 | Release and extraction of cfDNA from the blood. cfDNA is released from healthy, inflamed or diseased (cancerous) tissue from cells undergoing apoptosis or necrosis. cfDNA can be extracted from a blood sample and genetic aberrations in the DNA released from cancerous tissue detected and quantified. Tumour-derived genetic alterations that can be detected in the blood include point mutations (consecutive purple, red, green and blue DNA strands), copy number fluctuations (red portion of chromosomes) and structural rearrangements (green and red DNA strands). Abbreviations: cfDNA, circulating free DNA; ctDNA, circulating tumour DNA.

Crowley, Nature Rev Clin Oncology 2013

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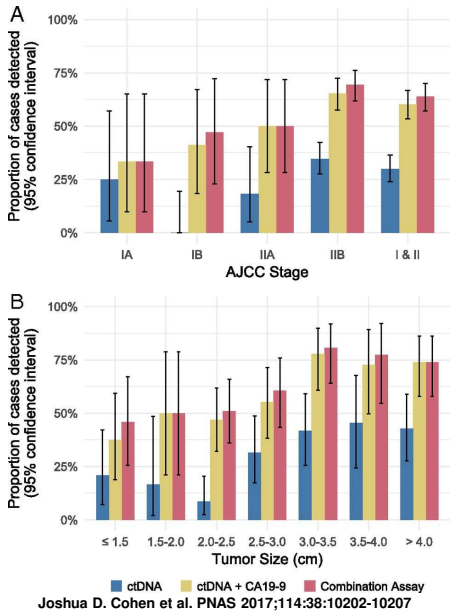
Combining ctDNA KRAS mutations with protein biomarkers



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Joshua D. Cohen et al. PNAS 2017;114:38:10202-10207

PNAS

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Surveillance of familial relatives- CAPS study

- Multicenter: JHU, Penn, U Pitt, Dana Farber, Case Western, Columbia, Yale.
- Enrollment Criteria:
  - Age: FPC :>= 55 years
  - 10 years younger than youngest PC
  - Germline mutation carriers
- Cases: Asymptomatic

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Surveillance of familial relatives- CAPS study

- 354 relatives with regular follow-up, mean age 61, range 51.8-68.4
- 52% male, mean follow-up time of 5.43 years (0.5-14.8 years).
- 29 had radiological progression
- 27 had neoplastic progression:
- 13 progressed to PDAC, PanNET (5) or high-grade dysplasia
- Overall, the rate of neoplastic progression was 1.6% per year.

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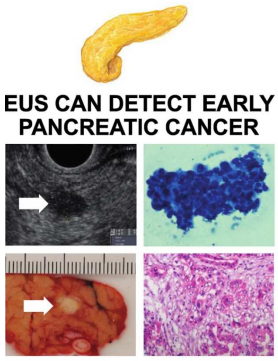


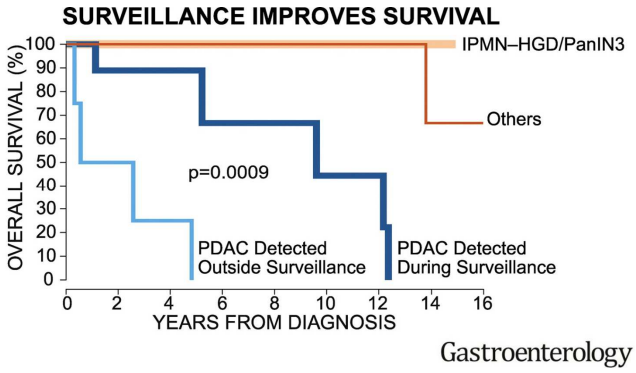
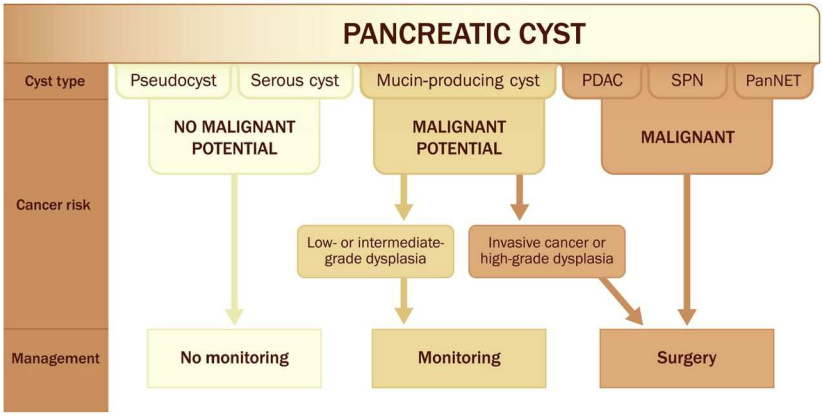


Fig. 3 Clinical management of patients with pancreatic cysts.



Simeon Springer et al., Sci Transl Med 2019;11:eaav4772

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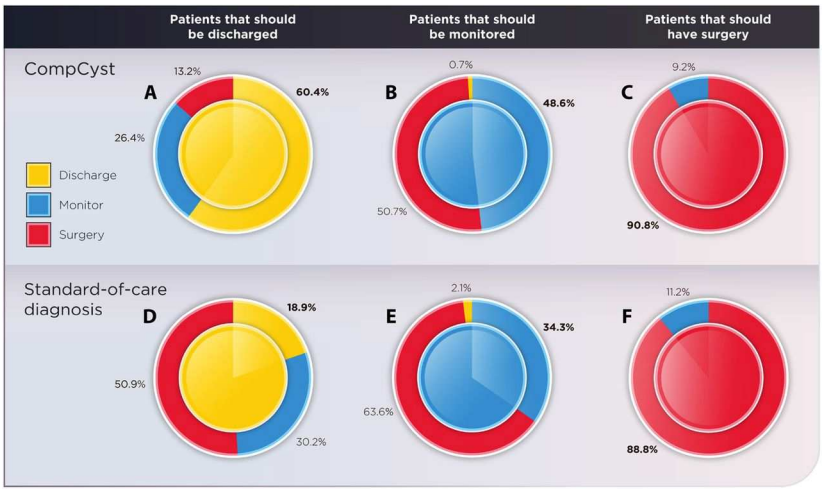
Fig. 4 Management of pancreatic cysts.



Simeon Springer et al., Sci Transl Med 2019;11:eaav4772

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For more information

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- PANCAN – patientcentral@pancan.org
- National Familial Pancreas Tumor Registry / Cancer of the Pancreas Screening study – pancreas@jhmi.edu
- GENERATE – www.generatestudy.org

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THANK YOU FOR YOUR PARTICIPATION

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