Genetics of Pancreatic Cancer

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Topics

- Is family history a risk factor for pancreatic cancer?
- Why we study families with pancreatic cancer
- New discoveries in genetics of pancreatic cancer: What does it all mean?

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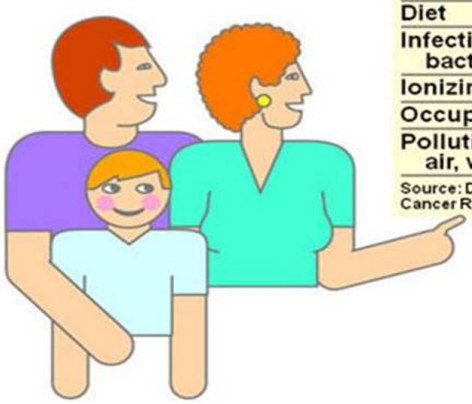
Avoidable Risk Factors



Proportion of Cancer Deaths Linked to Avoidable Risk Factors

Tobacco	29–31 percent
Diet	20–50 percent
Infections: bacteria, viruses	10–20 percent
Ionizing and UV light	5–7 percent
Occupation	2–4 percent
Pollution: air, water, food	1–5 percent

Source: Doll R. (UK data) Recent Results in Cancer Research 1998; 154:3-21.

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Pancreatic Cancer: Risk Factors

Smoking
Cigarette smokers are two or three times more likely than nonsmokers to develop pancreatic cancer

Dietary
Diets low in fruits and vegetables can increase risk of developing panceatic cancer

Diabetes

Chronic pancreatitis

Age
Most pancreatic cancers occur in people over the age of 60

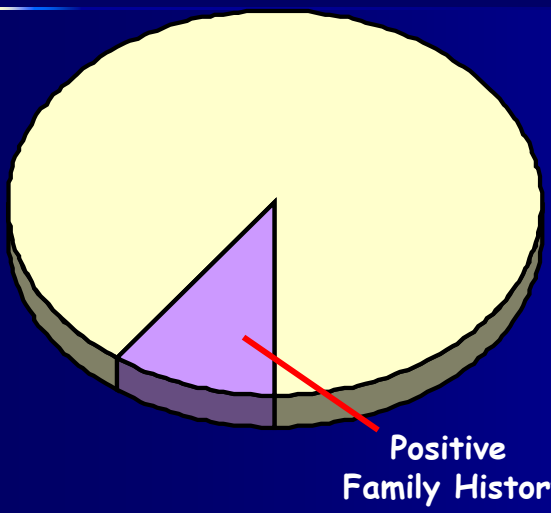
Being male
More men than women are diagnosed with pancreatic cancer

Being African American
African Americans are more likely than Asians, Hispanics, or whites to get pancreatic cancer

Family history
The risk for developing pancreatic cancer triples if a person's mother, father, sister, or brother had the disease

Genes and/or Shared environment?

10% of pancreatic cancer patients have a first degree relative with pancreatic cancer



- The same proportion, 10% is seen for other major cancers (breast, colon, prostate, lung)
- Susceptibility genes have been identified for some subsets of these cancers
- Similarly, pancreatic cancer may have susceptibility genes

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Genetics and Your Family History

- Is family history a risk factor for pancreatic cancer?
- Why we study families with pancreatic cancer
- New discoveries in genetics of pancreatic cancer: What does it all mean?

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In the clinic, knowing about your family history is one way to:

- Identify who is at risk
- Refer for genetic risk counseling and possibly genetic testing
- Recommend who needs checkups more often

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Family-based Research

- Patient provides family history information: at least three generations is helpful
- Family members can be invited into the study
- Even deceased relatives are important!
- DNA from blood, combined with the family history structure, helps to "connect the dots"

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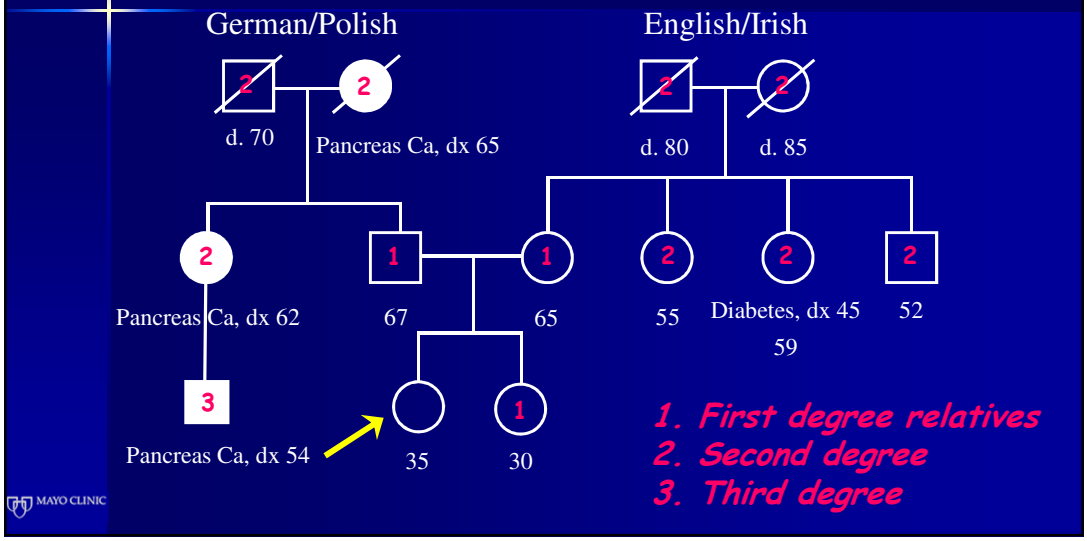
Three-Generation Family Tree



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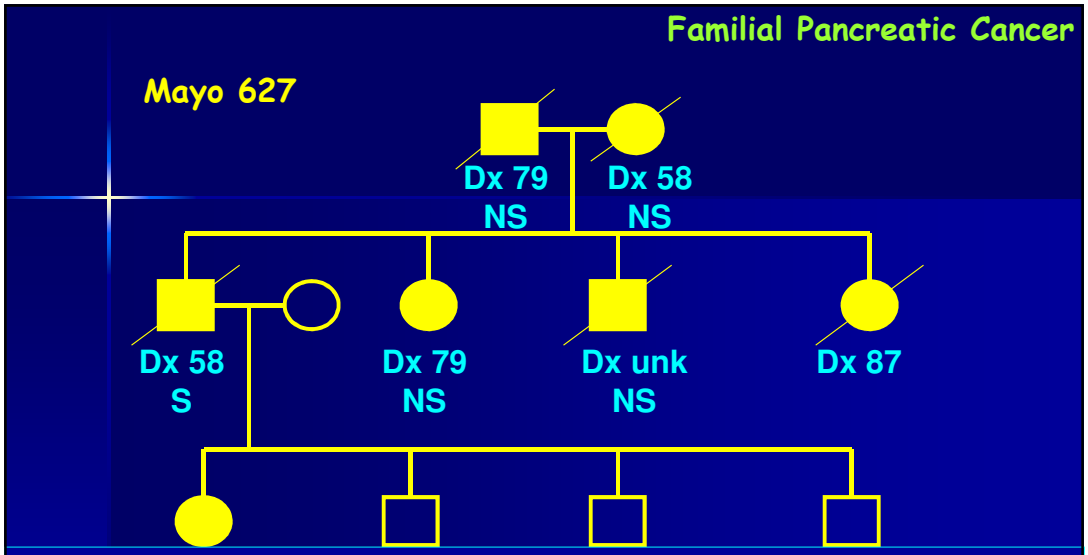
Familial Pancreatic Cancer

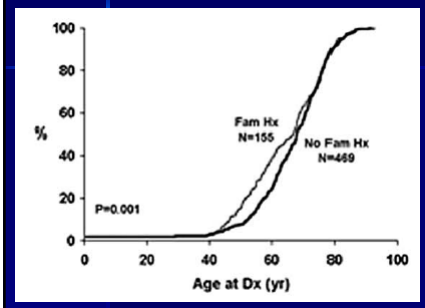


Working definition:

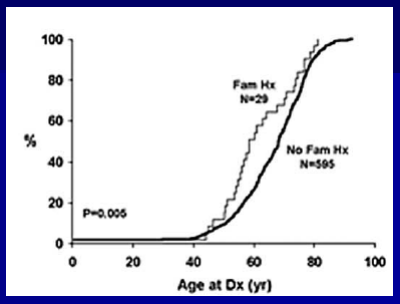
Families in which at least two first degree relatives have been diagnosed with pancreatic cancer.

Hruban and Petersen, 1997

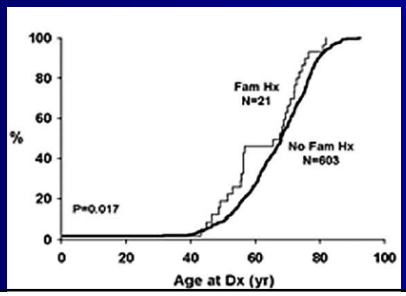
Family history of some cancers is associated with younger age of onset of pc



Breast Cancer



Ovarian Cancer



Melanoma

McWilliams RR et al. Clin Gastro Hepatol 4:1143, 2006

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Hereditary Disorders and Genes Associated with Pancreas Cancer

Disorder	Gene
Hereditary Pancreatitis	PRSS1 (Cationic trypsinogen)
Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)	P16 (CDKN2A)
BRCA2	BRCA2
Hereditary Colorectal Cancers	APC, MSH2, MLH1
Peutz-Jeghers Syndrome	STK11/LKB1
Fanconi Anemia genes	FANCC, FANCG

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TABLE 1 Inherited cancer predisposition syndromes that increase the risk for pancreatic cancer

Syndrome	Gene(s)	Risk of PC	Predominant Features
Hereditary breast and ovarian cancer	*BRCA1*	RR, 2.26–3.0	Malignancies: breast (particularly premenopausal), ovary, male breast, prostate
	BRCA2	RR, 3.5–5.9	Malignancies: breast (particularly premenopausal), ovary, male breast, prostate, melanoma (cutaneous and ocular)
Familial atypical mole and melanoma	*CDKN2A*	RR, 7.4–47.8	Malignancies: melanoma (often multiple and early onset) Other: dysplastic nevi
Hereditary pancreatitis	*PRSS1*	SIR, 57	Other: chronic pancreatitis
Hereditary nonpolyposis colorectal cancer (Lynch syndrome)	*MLH1* *MSH2* *MSH6* *PMS2* *EPCAM*	SIR, 0–8.6	Malignancies: colorectum, endometrium, ovary, stomach, small bowel, urinary tract (ureter, renal pelvis), biliary, brain (glioblastoma), skin (sebaceous)
Peutz Jeghers Syndrome	*STK11*	SIR, 132	Malignancies: colorectum, small bowel, stomach, breast, gynecological Other: melanin pigmentation (mucocutaneous), small-bowel intussusception

SIR indicates standardized incidence ratio; RR, relative risk.

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Axilbund,J, Wiley E. Genetic Testing by Cancer Site: Pancreas. Cancer Journal. 18(4):350-354, 2012.

Genetics and Your Family History

- Is family history a risk factor for pancreatic cancer?
- Why we study families with pancreatic cancer
- New discoveries in genetics of pancreatic cancer: What does it all mean?

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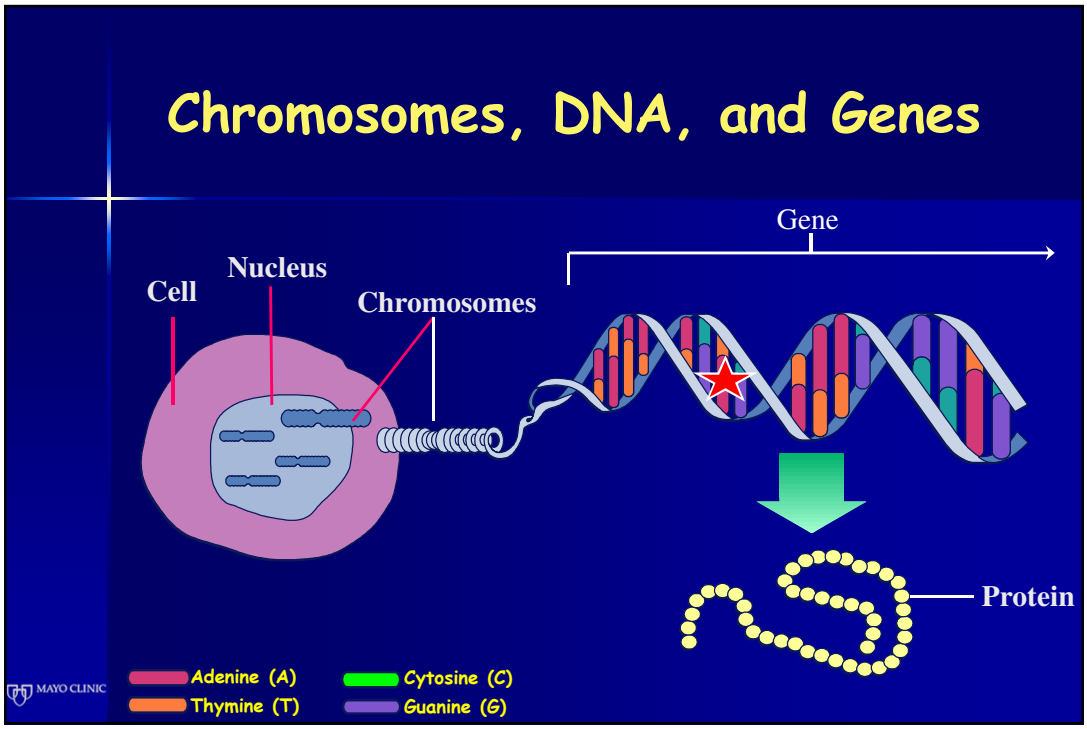
Who is at risk for pancreatic cancer?.


Genetics provides a clue…


Chromosomes, DNA, and Genes
Gene
Nucleus
Cell
Chromosomes
Protein
Adenine (A)
Thymine (T)
Cytosine (C)
Guanine (G)
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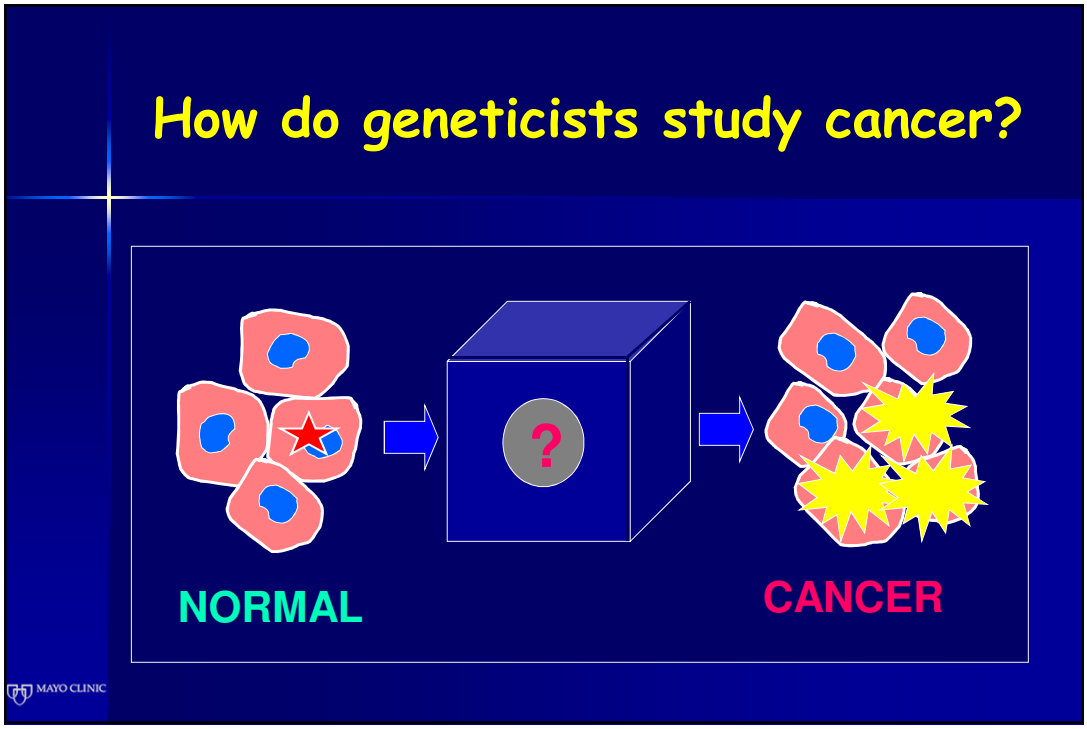
How do geneticists study cancer?
?
NORMAL
CANCER
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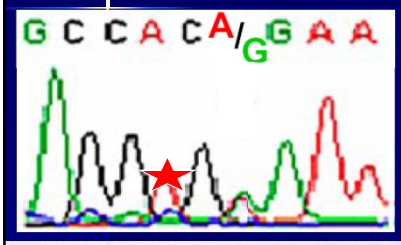
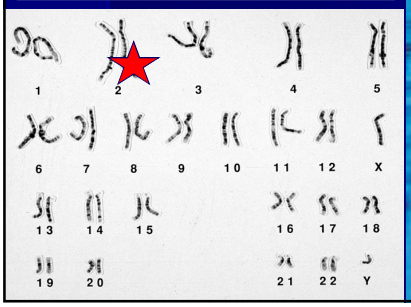
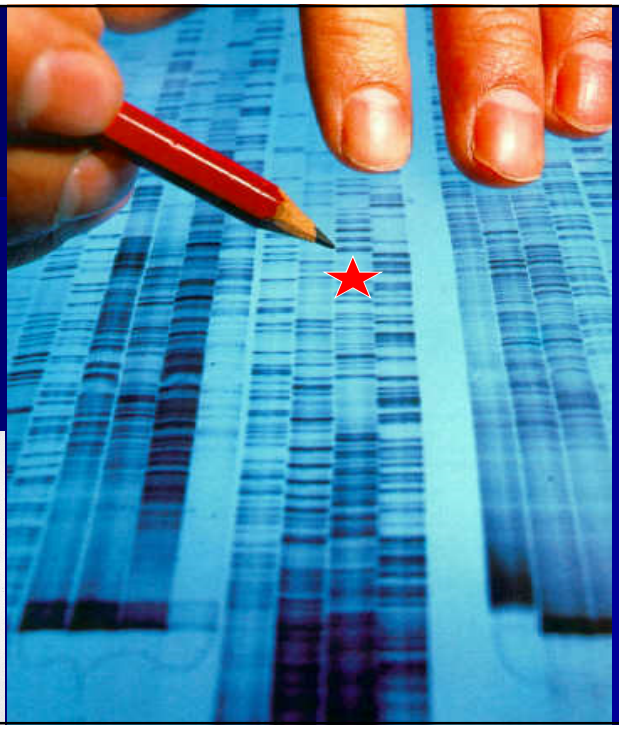
DNA Sequencing







Is There A Genetic Connection Between Melanoma and Pancreatic Cancer?

- **Methods:**
  - 1,537 pancreatic adenocarcinoma patients
  - Mutation analysis of *CDKN2A* gene
- **Results:**
  - 9 (0.6%) carried germline mutations in *CDKN2A*
  - Carriers were more likely to have:
    - Family history of pancreatic cancer (p= 0.003); carrier rate 3.3%
    - Family history of melanoma (p= 0.03); carrier rate 5.3%
    - Personal history of melanoma (p= 0.01)

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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

Pt	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

* M= male, F=female, age (years) at diagnosis of pancreatic cancer, AAC = amino acid change

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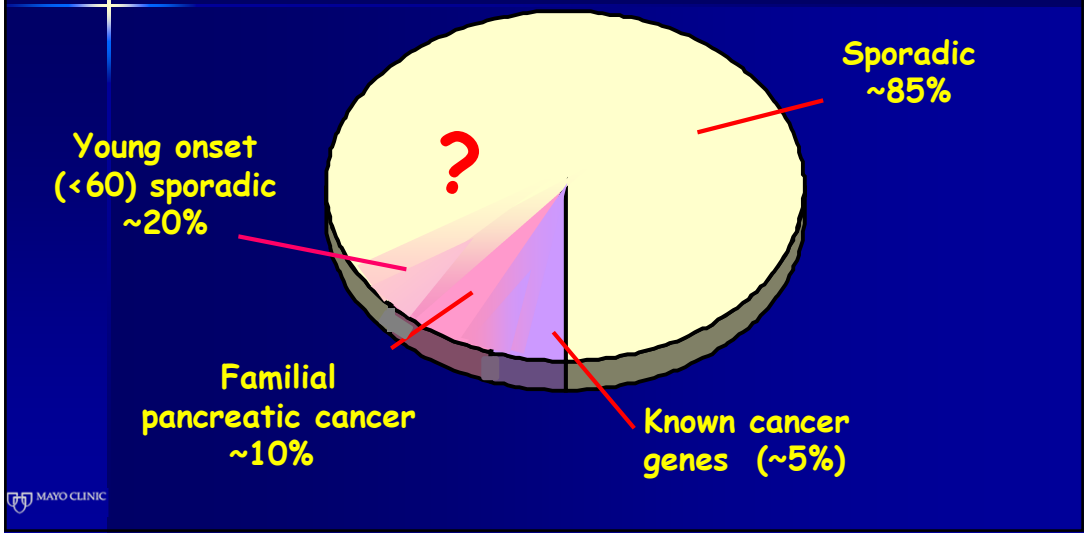
McWilliams RR et al. Eur J Hum Genetics, 2011 Apr;19(4):472-8.

Genetic susceptibility to pancreatic cancer



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PanScan – a GWAS

- PanScan 1
  - Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, et al. Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer. *Nature Genetics* 41:986-90, September, 2009.
  - 2000 pairs
- PanScan 2
  - Petersen GM, Amundadottir A, Fuchs CS, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. Nature Genetics, Feb 2010.
  - 3,850 pairs

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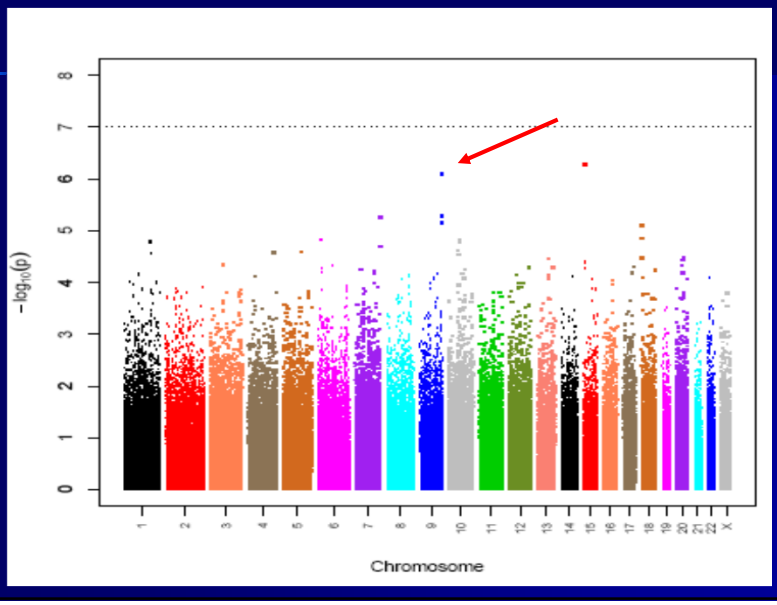
GWAS Results: ABO Blood Group



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ABO Blood Groups and Cancer

- **Gastric Cancer - well established**
  - Increased risk for blood group A
- **Pancreatic Cancer** -Possibly risk with ABO

Disease	ABO allele	↑ Risk	χ^2
Duodenal ulcer	O	1.40	200
Stomach cancer	A	1.25	49
Stomach ulcer	O	1.82	37
Pernicious anemia	A	1.50	17
Pancreas cancer	A	1.27	8

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Bodmer and Bonilla Nat Gen 2008

Summary of GWAS Main Findings

- **Chromosome 13q22.1** - 2 SNPs: **rs9543325** (*P*=3.27x10-11; per allele odds ratio, OR 1.26, 95% CI=1.18-1.35) and **rs9564966** (*P*=5.86x10-8; per allele OR 1.21, 95% CI=1.13-1.30) map to a non-genic region
- **Chromosome 1q32.1** – 5 SNPs map to *NR5A2* [Nuclear receptor subfamily 5, group A, member 2] ; the strongest signal was **rs3790844** (*P*=2.45x10-10; per allele OR 0.77, 95% CI=0.71-0.84).
- **Chromosome 5p15.33** – 1 SNP maps to *CLPTM1L-TERT*; **rs401681** (*P*=3.66x10-7; per allele OR 1.19, 95% CI=1.11-1.27) ; gene is associated with multiple cancers.

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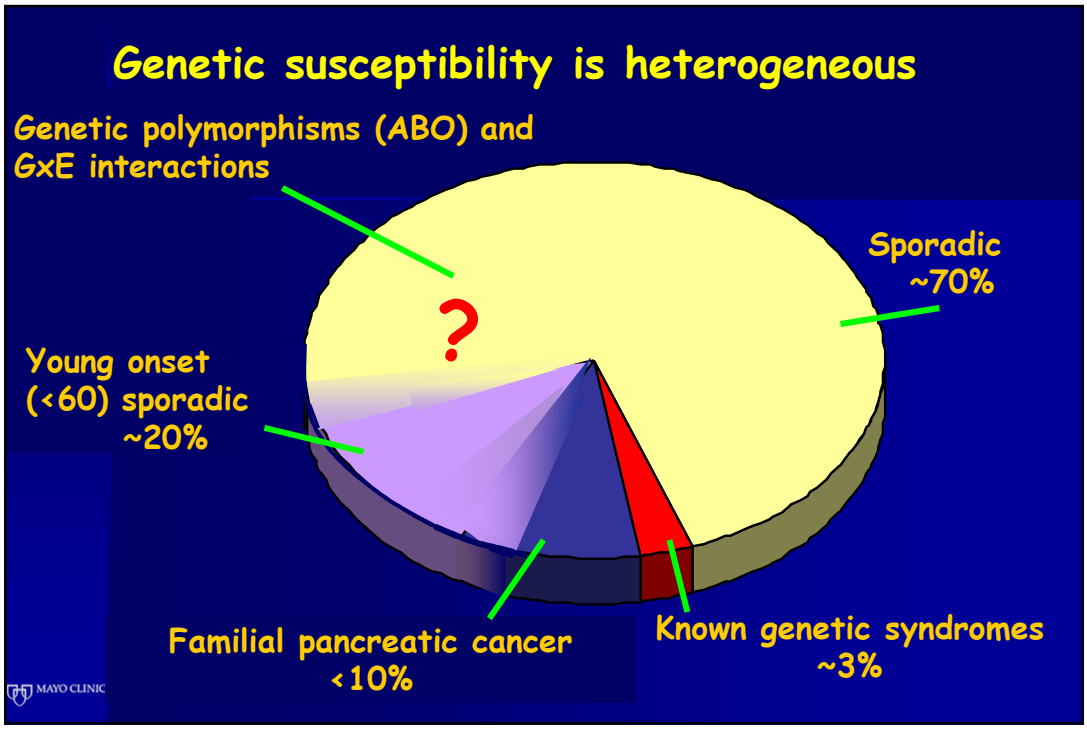
Genetic susceptibility is heterogeneous
Genetic polymorphisms (ABO) and GxE interactions
?
Sporadic ~70%
Young onset (<60) sporadic ~20%
Familial pancreatic cancer <10%
Known genetic syndromes ~3%
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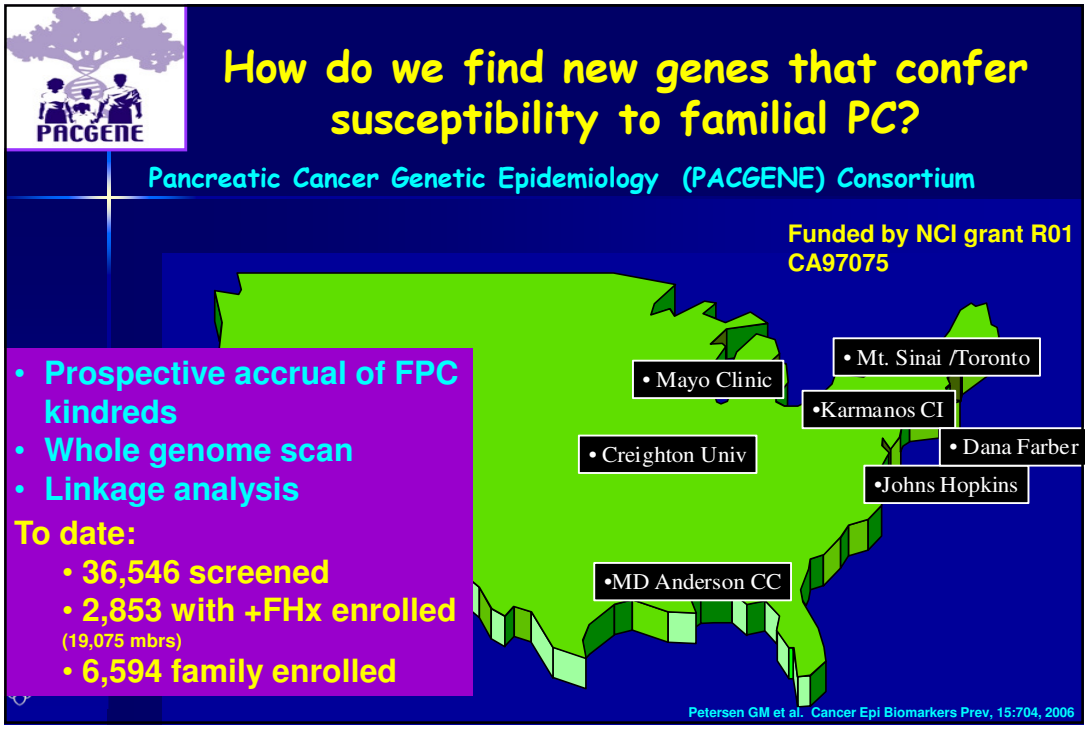
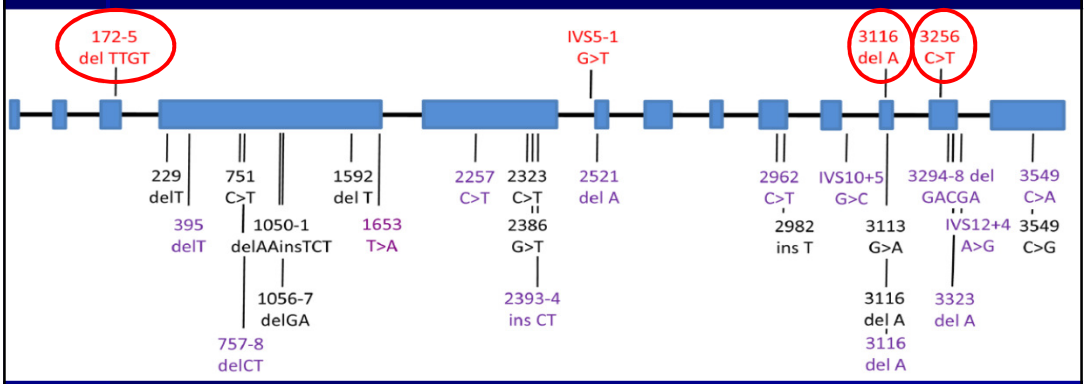

PACGENE
How do we find new genes that confer susceptibility to familial PC?
Pancreatic Cancer Genetic Epidemiology (PACGENE) Consortium
Funded by NCI grant R01 CA97075
• Prospective accrual of FPC kindreds
• Whole genome scan
• Linkage analysis
To date:
• 36,546 screened
• 2,853 with +FHx enrolled (19,075 mbrs)
• 6,594 family enrolled
• Mayo Clinic
• Mt. Sinai /Toronto
•Karmanos CI
• Creighton Univ
• Dana Farber
•Johns Hopkins
•MD Anderson CC
Petersen GM et al. Cancer Epi Biomarkers Prev, 15:704, 2006

New familial pancreatic cancer gene: PALB2



- 96 FPC patients screened for PALB2 mutations (90 Caucasian)
- Average onset age: 66.7 years (in non PALB2 kindreds, 65.3)
- Previous published study: no mutations in 1,084 normal controls.

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Jones S, Hruban RH, Kamiyama M, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. Science, 324:217, 2009.

ATM gene mutations predispose some families to pancreatic cancer

- Ataxia telangiectasia mutated (ATM) gene, a serine/ threonine kinase
- Coordinates DNA double-strand break repair
- Causes AT (autosomal-recessive)
- Associated with an increased risk of cancer, particularly lymphoma and leukemia

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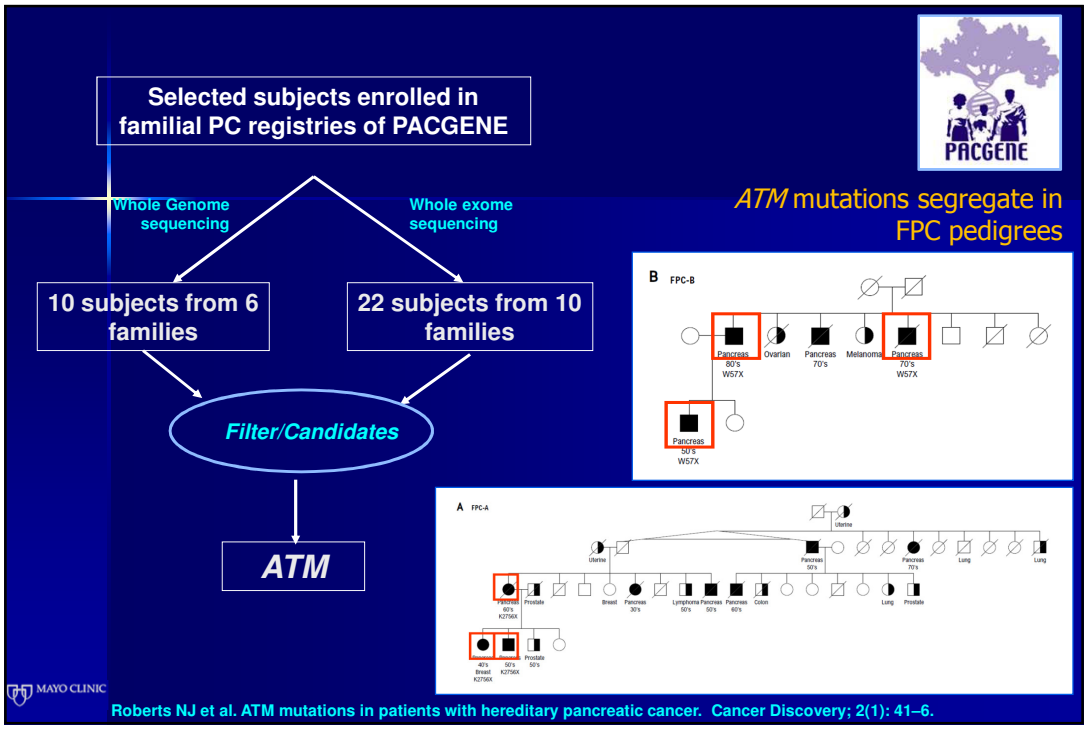
Roberts NJ et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discovery; 2(1): 41-6, 2012.



Functional ATM variants

Table 2. Summary of heterozygous deleterious *ATM* variants found in patients with pancreatic cancer

Variant	Pancreatic cancer type	Nucleotide (genomic)[a]	Nucleotide (cDNA)[b]	Amino acid (protein)[c]	Type	Number of affected individuals sequenced
1	Familial[d]	g.chr11:107711896A>T	c.8266A>T	p.K2756X	Nonsense	3
2	Familial[e]	g.chr11:107603810G>A	c.170G>A	p.W57X	Nonsense	3
3	Familial	g.chr11:107648719G>T	c.3214G>T	p.E1072X	Nonsense	1
4	Familial	g.chr11:107691848G>A	c.6095G>A	p.R2032K	Missense	1
5	Familial	g.chr11:107693309G>T	IVS41-1G>T	sp	Splice site	1
6	Familial	g.chr11:107660218delG	c.3801delG	fs	INDEL	1

- 4/166 (2.4%) carried deleterious ATM mutations. 0/190 controls. P=0.046
- For probands≥3 in family: 4.6%
- ATM contributes to the genetic heterogeneity of familial pancreatic cancer

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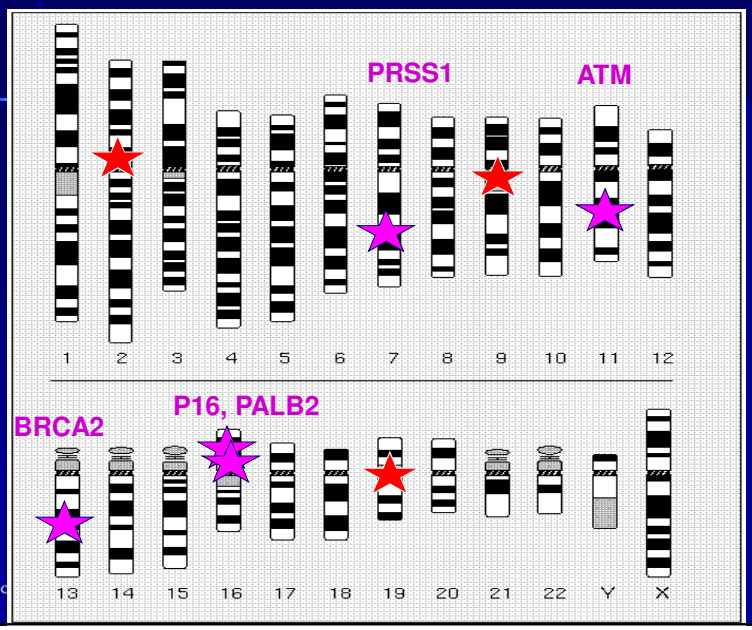
Roberts NJ et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discovery; 2(1): 41-6, 2012.

Where are genes for inherited pancreatic cancer?



Others:
- FANCC (9q)
- CFTR (7q)
- PJS (19p)
- MMR (2p, 3p)
- APC (5q)
- PALLD (4q)

At least 3 other genomic regions involved

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Genetics and Your Family History

- Is family history a risk factor for pancreatic cancer?
- **What does it all mean?** ies with pancreatic cancer
- New discoveries in genetics of pancreatic cancer

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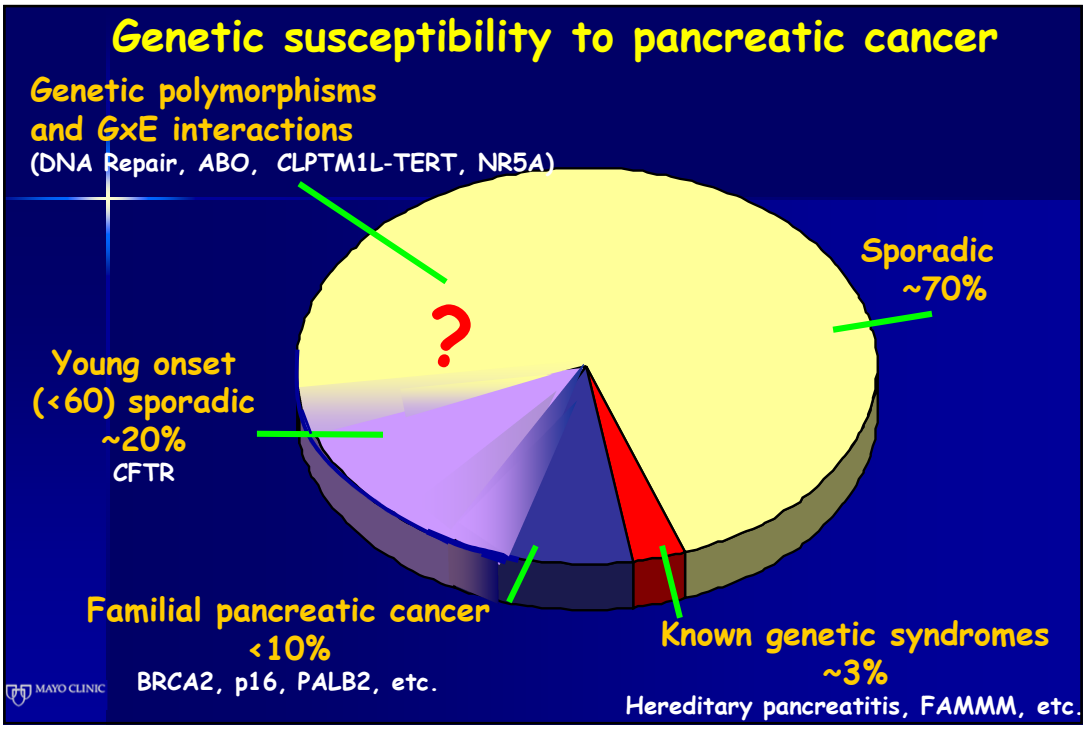
Genetic susceptibility to pancreatic cancer



Inherited Susceptility to Pancreatic Cancer: Updated

Genes	Risk of pancreatic cancer
BRCA2 ✔	OR = 3.5 (95% CI = 1.87–6.58)
STK11	SIR = 132 (95% CI = 44–261)
PALB2 ✔	Increased
PRSS1 and *SPINK1*	SIR = 67 (95% CI = 8–80)
ATM	Increased
CDKN2A ✔	SIR = 13–38
Unknown*	SIR = 6–32
Mismatch repair genes (*MLH1*, *MSH2*, *MHS6* and *PMS2*)	No effect up to SIR = 8.6 (95% CI = 4.7–15.7)
BRCA1 ✔	No effect up to OR= 2.26 (95% CI = 1.26–4.06)

CI, confidence interval; OR, odds ratio; SIR, standardized incidence ratio. *Kindred with familial pancreatic cancer but without mutations in an established pancreatic cancer gene.

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Klein AP. Identifying people at a high risk of developing pancreatic cancer. Nat Rev Cancer. 2013 Jan;13(1):66-74.

Frequencies of *BRCA1*, *BRCA2*, *CDKN2A*, and *PALB2* Germline Mutations in Familial Pancreatic Cancer (FPC): A PACGENE Study.

Zhen DB, Rabe KG, Gallinger S, Syngal S, Schwartz AG, Goggins MG, Hruban RH, Cote ML, Moyes K*, Wenstrup RJ*, Hartman A-R*, Seminara D, Klein AP, Petersen GM. (*Myriad Genetics). American Society of Human Genetics Annual Meeting Poster 3433T, October 2013.

- Five PACGENE sites contributed germline DNA samples from 518 unrelated cases affected with pancreatic adenocarcinoma.
- Tested individuals were affected with pancreatic cancer (PC) and all came from kindreds with 2+ PC
- 160 individuals were from kindreds that met criteria for FPC; the remainder were Non-FPC.
- Testing performed on *BRCA1*, *BRCA2* (including analysis of deletions and arrangements), *CDKN2A*, and *PALB2*.
- Mutation frequencies in subset of patients who had had all 4 genes tested

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Pancreatic Cancer Cases Tested for All Four Genes

Gene	D/S (%)		VUS (%)	
	FPC (N=154)	Non-FPC (N=336)	FPC (N=154)	Non-FPC (N=336)
BRCA1	2.0	0.6	0	0
BRCA2	3.3	3.0	0	0.9
CDKN2A	2.6	0.9	5.2	1.2
PALB2	0.7	0.3	0	2.1
Total (probability of a mutation in any of the four genes)	**7.8**	**4.8**	**5.2**	**4.2**

FPC : Familial Pancreatic Cancer (2+ affected first degree relatives in kindred)

Non-FPC: Two affected blood relatives in kindred, not first degree

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Lucas AL et al. BRCA1 and BRCA2 germline mutations are frequently demonstrated in both high-risk pancreatic cancer screening and pancreatic cancer cohorts. Cancer, April 2014 epub ahead of print.

- High risk genetics/prevention setting for PC
- N=37 high risk unaffected individuals
- 7 (18.9%) positive
- N=32 patients affected with PC
- 7 (21.9%) positive
- High proportion of Ashkenazi Jewish (AJ) population; recommended that BRCA1/2 testing should be considered in AJ PC patients even with no family history of breast or ovarian cancer

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Lucas AL et al. BRCA1 and BRCA2 germline mutations are frequently demonstrated in both high-risk pancreatic cancer screening and pancreatic cancer cohorts. Cancer, April 2014 epub ahead of print.

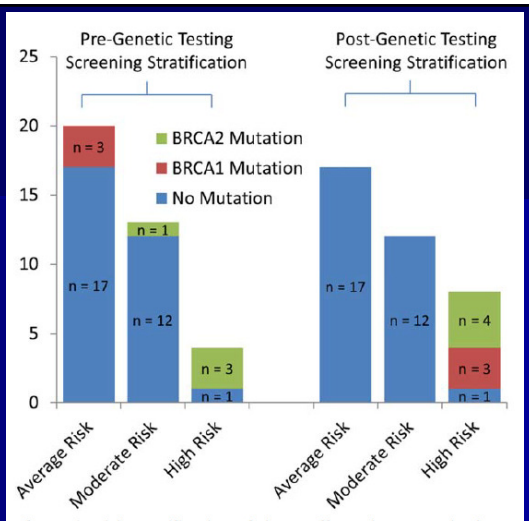

Figure 2. Risk stratification of the unaffected pancreatic ductal adenocarcinoma screening cohort who underwent genetic testing at the study institution is shown. Risk stratification before genetic testing identified 20 patients at average risk, 13 patients at moderate risk, and 4 patients at high risk. Of the 4 high-risk patients, 3 (75%) were *BRCA2* carriers. One moderate-risk patient was found to carry a *BRCA2* mutation. A total of 3 of 20 average-risk patients (15%) were found to have *BRCA1* mutations. All *BRCA1/2* mutation carriers were reclassified into a high-risk screening protocol.

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Conclusions

- Research has shown that there are individuals at increased risk for developing pancreatic cancer
- Genetic susceptibility is heterogeneous
- Limited genetic testing is available
- Our work continues to better understand the genetics and to help patients

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Collaborators & Acknowledgments

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PACGENE collaborators
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