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Hereditary Pancreatic Cancer

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No conflicts of interest

Objectives/Agenda

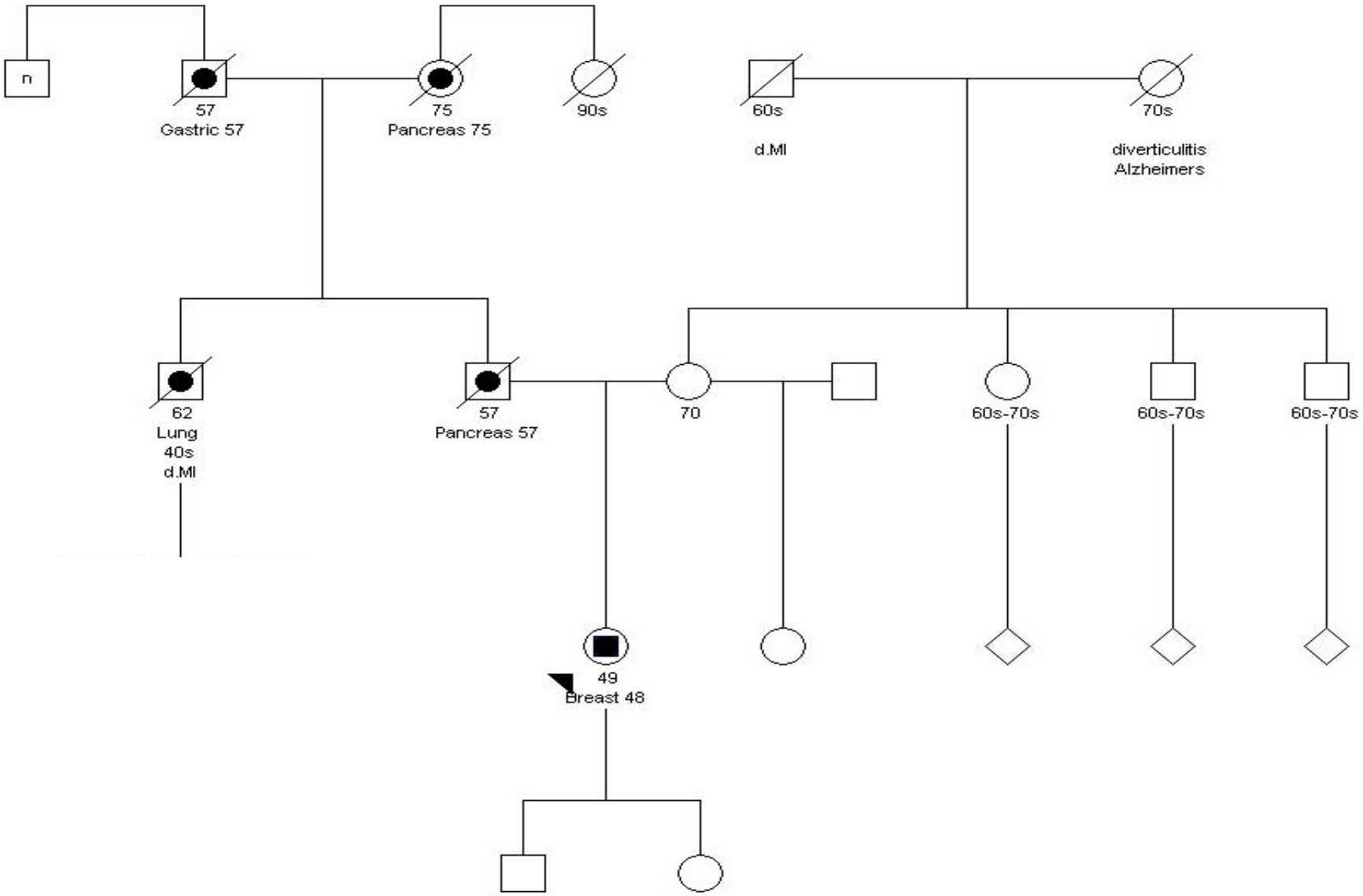
- Identify patients who may benefit from genetic testing
- Identify hereditary cancer syndromes associated with an increased risk to develop pancreatic cancer
- Discuss considerations for pancreatic cancer screening based on hereditary risk factors

Background

- Historically, genetic etiologies of pancreatic cancer were poorly understood, despite familial patterns

- Guidelines for germline genetic testing with respect to pancreatic cancer have evolved → more testing is being performed → increased understanding of hereditary contributions

- Germline genetic testing results may impact treatment for patient and provide important information for the family


n
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Gastric 57
75
Pancreas 75
90s
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d.MI
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diverticulitis
Alzheimers
62
Lung
40s
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Pancreas 57
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60s-70s
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60s-70s
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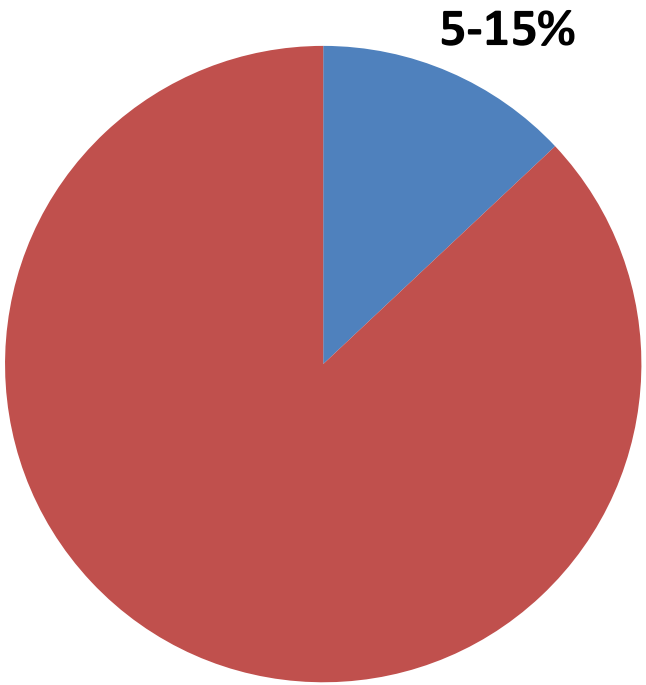
Breast 48

Hereditary Pancreatic Cancer



- Several familial cancer syndromes are associated with an increased risk for pancreatic cancer
- Several single genes have been associated with increased risk for pancreatic cancer

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Known Hereditary Cancer Syndromes Linked with Pancreatic Adenocarcinoma Risk

Syndrome	Lifetime Risk for Pancreatic Cancer	Other Cancers/Symptoms	Gene
Hereditary Pancreatitis	**40%**	**Pancreatitis (inflammation/scarring of pancreas)**	**PRSS1, SPINK1, CFTR**
Peutz-Jeghers	**~36%**	**Small bowel cancer, gastric cancer, ovarian cancer, skin freckling**	**STK11**
Familial Atypical Multiple-Mole Melanoma	**17%**	**Melanoma, multiple atypical moles**	**P16/CDKN2A**
Hereditary Breast-Ovarian Cancer	~4 %(BRCA1) ~5-9% (BRCA2)	Breast cancer, ovarian cancer, male breast cancer	BRCA1, BRCA2
Li-Fraumeni Syndrome	~11%	Breast cancer, sarcomas, adrenal cortical carcinoma	TP53
Lynch	Up to 6%	Colon, endometrial, ovarian, stomach cancers	MLH1, MSH2, MSH6, PMS2, EPCAM
Familial Adenomatous Polyposis	2%	Colon cancer, multiple colon polyps, small bowel cancer, skin tumors	APC

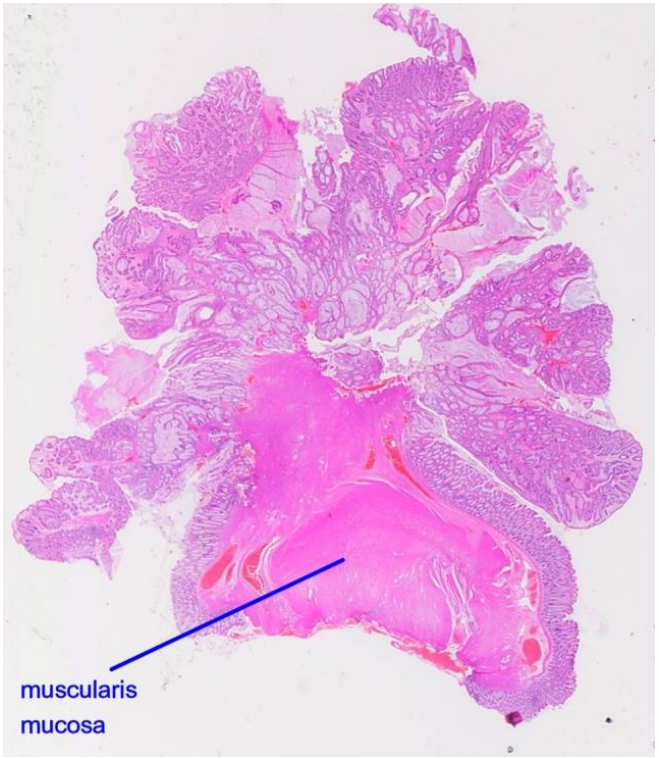
Known Hereditary Cancer Syndromes Linked with Pancreatic Neuroendocrine Tumors

Syndrome	Lifetime Risk for Pancreatic Neuroendocrine Tumors	Other Cancers/Symptoms	Gene
Multiple Endocrine Neoplasia, Type 1	**40-70%**	**Pituitary adenoma, parathyroid hyperplasia, skin findings**	**MEN1**
Von Hippel Lindau	**5-17%**	**parganglioma, phyeomcyomctoms, hemagioblatimas, cystadenoma,**	**VHL**
Neurofibromatosis Type 1	Rare	Neurofibromas, skin lesions (CAL and freckling), Lisch nodules, Glioma, GIST	NF1
Multiple Endocrine Neoplasia, Type 4	?	Parathyroid adenoma/hyperplasia, Pituitary adenomas, duodenal NETs, Papillary thyroid carcinoma	CDKN1B
Tuberous Sclerosis Complex	Rare	Skin lesions, renal angiolipoma, CNS tumors/cancer, clear cell renal carcinoma, Cardiac rhabdomyoma	TSC1/TSC2
Hereditary Paraganglioma-Pheochromocytoma Syndrome	Case reports	paraganglioma , pheochromocytoma, GIST, renal cell cancer	MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127

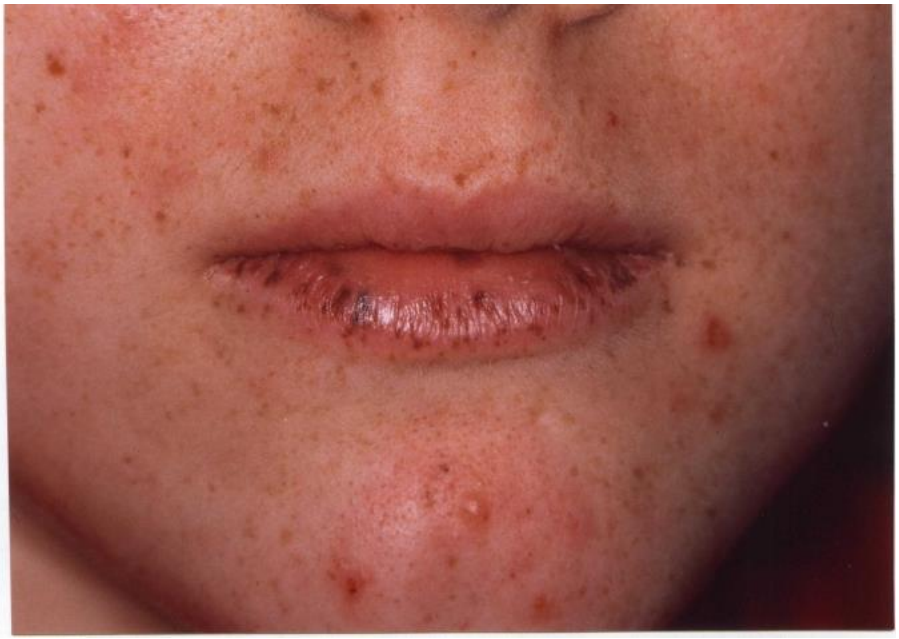
Genes	Syndrome	Cancer Risks
ATM		Breast, Pancreas, Prostate
APC	FAP	Colon
BRCA1/BRCA2	HBOC	Breast, Ovary
CHEK2		Breast, Prostate
CDNK2A	FAMMM	Melanoma, Pancreas
MLH1/MSH2/ PMS2/MSH6/ EPCAM	Lynch	Colon, Uterine, Ovarian
PALB2		Breast, Pancreas, Ovarian
TP53	Li-Fraumeni	Breast, Sarcoma, Brain
STK11	Peutz-Jeghers	Breast, Colon, Pancreatic, Gastric, Lung

Peutz-Jeghers Syndrome

- Hamartomatous polyps of the GI tract



- Mucocutaneous hyperpigmentation



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http://www.ncbi.nlm.nih.gov/books/NBK26374/

FAMMM (Familial Atypical Mole and Multiple Melanoma)

	p16-Leiden positive
Number of atypical nevi	Any number
Risk of melanoma	80-100%
Risk of pancreatic cancer	**17%**

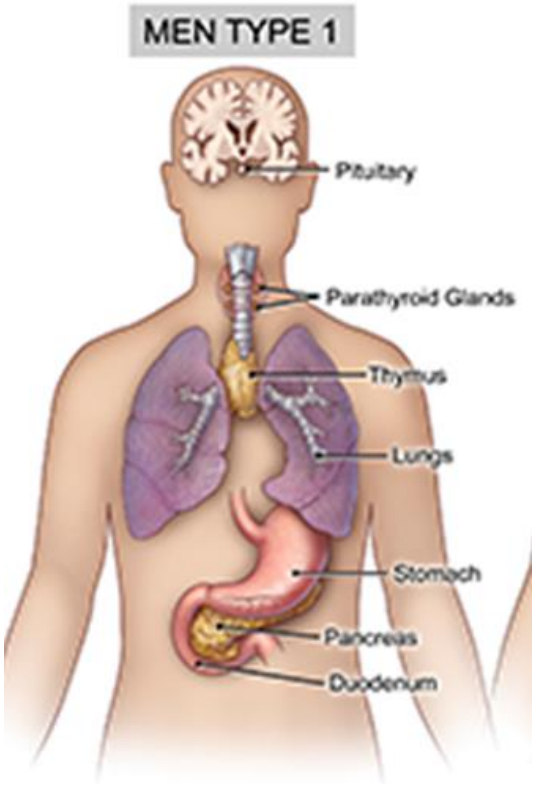
- 16% of p16-Leiden mutation carriers with pancreatic cancer were diagnosed < age 45
- In familial PC family with one or more cases of melanoma – 40% p16 mutation
- Sporadic PC - ~2% p16 mutations

Multiple endocrine neoplasia type 1 (MEN1)

Clinical Diagnosis - two or more of following three tumors:

- Parathyroid tumors (90-100%)
  - Typically first feature
- Pituitary tumors (10-60%)
  - Prolactinoma= most common
- Pancreatic endocrine tumors (30-75%)
  - Gastrinoma= most common

- Most tumors of the glands are benign
- 50% pts with MEN1 show symptoms by age 20
- ~100% by age 60
- DeNovo rate = 10%



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http://www.mdanderson.org/patient-and-cancer-information/cancer-information/cancer-types/multiple-endocrine-neoplasia/men-full.jpg

Hereditary Breast and Ovarian Cancer Syndrome

- BRCA2 mutations identified in 17% of families with 3 or > relatives with pancreatic cancer (National Familial Pancreatic Tumor Registry)
- BRCA2 mutations were found in 19% of European families with 2 or > first-degree relatives with pancreatic cancer
- Family history of breast/ovarian cancer may be absent in families with pancreatic cancer and a germline BRCA2 mutations

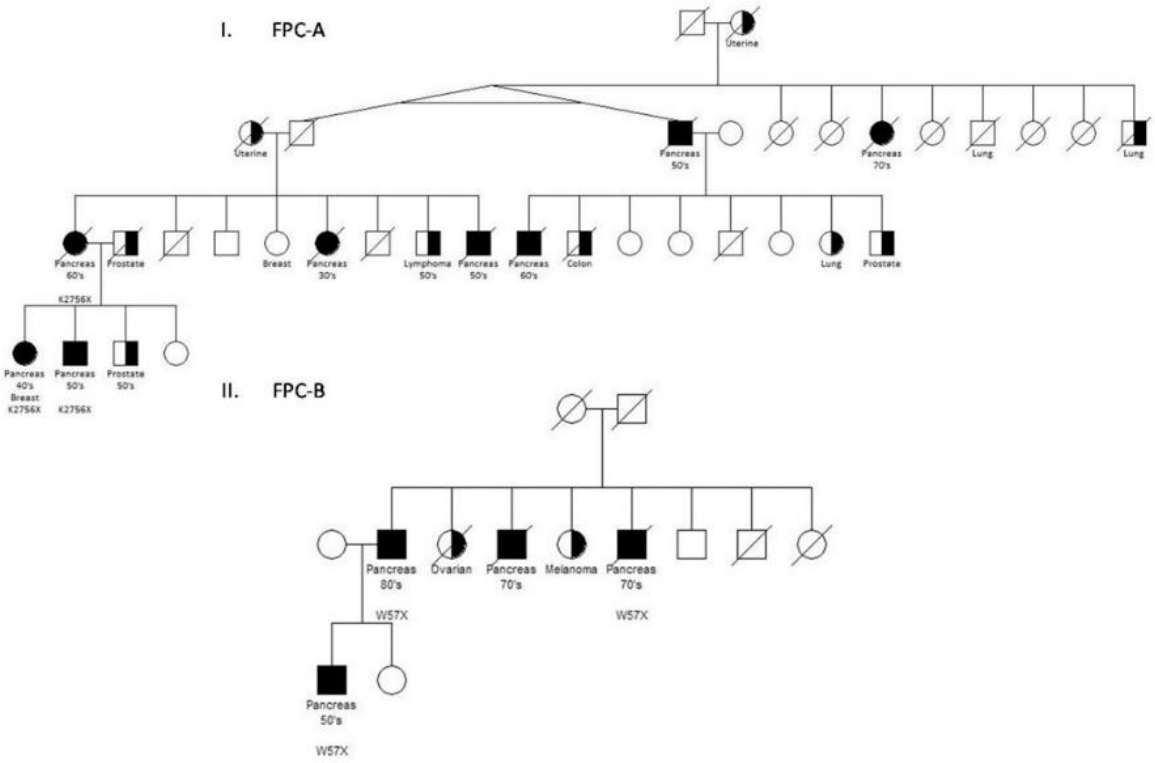
BRCA1/2 and Pancreatic Cancer

- BCLC demonstrate a 2-fold increase in risk for pancreatic cancer in BRCA1 mutation carriers

- BRCA2 mutations carriers have a 3-9 fold increased risk for pancreatic cancer

ATM and Pancreatic Cancer

166 unrelated familial pancreatic cancer patients, 2.4% (4/166) were found to have one ATM mutation and in families with 3 or more cases, 4.6% (4/87) carried a mutation (Roberts 2012)



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Pancreatic cancer in ATM carriers

Pancreatic cancer
RR of 2.41 (Thompson et al. J Natl Cancer Inst. 2005;97:813–822) RR of 3.92 (Geoffroy-Perez et al. Int J Cancer.. 2001 Jul 15;93(2):288-93)
Other cancers
Breast Prostate

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PALB2 (Partner And Localizer of BRCA2) and Pancreatic Cancer

- PALB2 mutations have been identified in a relatively small number (0.6%) of familial pancreatic cancer kindred
- Hofstatter et al. reported 2.1% of breast cancer patients with a family history of pancreatic cancer had a PALB2 mutation
- PALB2 mutations have not been identified in sporadic PC

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Antoniou AC, et al. (2014) N Engl J Med 371;6.

Pancreatic cancer in PALB2 carriers

Pancreatic cancer
RR of 2.37 (Yang et al. J Clin Oncol, 2020 Mar 1;38(7):674-685.)
Other cancers
Breast Possible ovarian cancer

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Referral to Genetics

- NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate - Version 3.2025
  - All individuals diagnosed with exocrine pancreatic cancer
  - First degree relatives of individuals diagnosed with an exocrine pancreatic cancer
  - Second degree relatives of individuals diagnosed with pancreatic cancer may meet criteria if there is additional family history of cancer (i.e. breast, ovarian, prostate)

Referral to Genetics

- NCCN Neuroendocrine and Adrenal Tumors - Version 1.2025
  - **Recommend** genetic evaluation for individuals with:
    - Clinical suspicion for *MEN1* due to
      - ≥2 of the following or 1 AND a family history of ≥1 of the following:
        - » Primary hyperparathyroidism
        - » Duodenal NET/PanNET
        - » Pituitary adenoma
        - » Foregut carcinoid (lung, thymic, or gastric)
    - Clinical suspicion for *MEN2* due to the presence of medullary thyroid carcinoma or other combination of MEN2-related features
  - **Consider** genetic evaluation for <u>all</u> individuals with pancreatic neuroendocrine tumors

Genetic Testing for Pancreatic Cancer

Original Article

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

Randall Brand, MD[1]; Erkut Borazanci, MD, MS[2]; Virginia Speare, PhD[3]; Beth Dudley, MS, MPH[1]; Eve Karloski, MS[1]; Mary Linton B. Peters, MD, MS[4]; Lindsey Stobie, MS[4]; Nathan Bahary, MD, PhD[1]; Herbert Zeh, MD[5]; Amer Zureikat, MD[5]; Melissa Hogg, MD[5]; Kenneth Lee, MD[5]; Allan Tsung, MD[5]; John Rhee, MD[1]; James Ohr, DO[1]; Weijing Sun, MD[6]; James Lee, MD, PhD[1]; A. James Moser, MD[4]; Kim DeLeonardis, MS[4]; Jill Krejdovsky, MS[4]; Emily Dalton, MS[3]; Holly LaDuca, MS[3]; Jill Dolinsky, RN, MS[3]; Arlene Colvin, MS[2]; Cynthia Lim, MS[2]; Mary Helen Black, PhD, MS[3]; and Nadine Tung, MD[4]

- The frequency of clinically actionable variant was 9.7%
- 80% were identified in PDAC-associated genes
- ATM was the most frequently mutated gene with a prevalence of 3.3%, and it was followed by BRCA1 and BRCA2 mutations combined, which were identified in 2.7% of the cohort

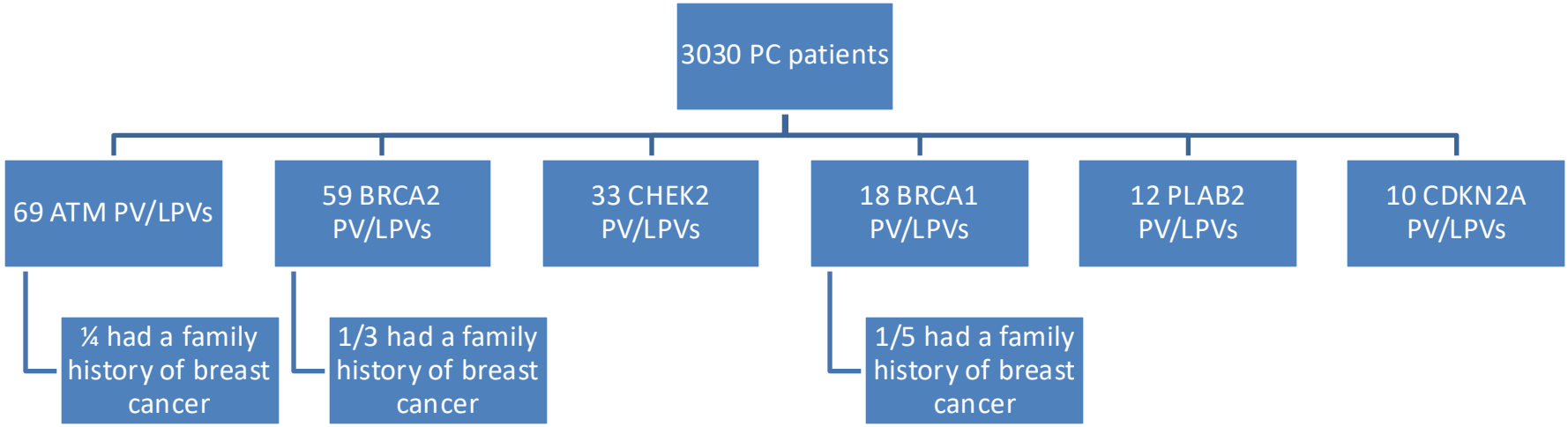
Cancer. 2018; 124, (17) , 3520-3527

Research

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; Karl 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



JAMA. 2018;319(23):2401-2409. doi:10.1001/jama.2018.6228

Genes Analyzed: ATM, BRCA1, BRCA2, BRIP1, CDKN2A, CHEK2, FANCC, MLH1, MRE11A, MSH2, NBN, NF1, PALB2, RAD51C, RAD51D, TP53

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Published in final edited form as:
Genet Med. 2018 January ; 20(1): 119–127. doi:10.1038/gim.2017.85.

PREVALENCE OF GERMLINE MUTATIONS IN CANCER GENES AMONG PANCREATIC CANCER PATIENTS WITH POSITIVE FAMILY HISTORY

Kari G. Chaffee, MS[1], Ann L. Oberg, PhD[1], Robert R. McWilliams, MD[2], Neil Majithia, MD[2], Brian A. Allen, MS[3], John Kidd, MS[3], Nanda Singh, PhD[3], Anne-Renee Hartman, MD[3], Richard J. Wenstrup, MD[3], and Gloria M. Petersen, PhD[1]

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[3]Myriad Genetics Laboratories, Inc., Salt Lake City, UT, 84108, U.S.A

- Myriad myRisk 25 gene panel completed on 302 patients with pancreatic adenocarcinoma
- 11.9% of patients carried a PV (ATM, BARD1, BRCA1, BRCA2, CDKN2A, CHEK2 ,MSH2, MUTYH, NBN, PALB2, PMS2)
- Overall prevalence of PVs among FPC (13.5%) patients versus non-FPC patients (9.4%)
  - * Kindreds with at least one pair of first degree relatives who were affected with PDAC were considered FPC and kindreds with at least two affected blood relatives that did not meet the FPC definition were considered "familial non-FPC".

Genetic Testing for PNET

Real-Time Genomic Characterization of Metastatic Pancreatic Neuroendocrine Tumors Has Prognostic Implications and Identifies Potential Germline Actionability

Table 2. Pathogenic or Likely Pathogenic Germline Alterations in 76 Cancer Predisposition–Associated Genes in Well-Differentiated Pancreatic Neuroendocrine Tumors

Gene	Mutation	HGVSp_Short	No. Patients (n = 17)	Penetrance and Significance
MEN1	c.773C>T	p.S258L	1	High penetrance
VHL	c.257C>T	p.P86L	1	High penetrance
TSC2	c.3598C>T	p.R1200W	1	High penetrance
CHEK2	c.1283C>T	p.S428F	1	Moderate penetrance
CHEK2	c.1337delA	p.N446Tfs*23	1	Moderate penetrance
CHEK2	c.470T>C	p.I157T	2	Moderate penetrance
Monoallelic *MUTYH*	c.494A>G	p.Y165C	2	Low penetrance
Monoallelic *MUTYH*	c.1419delC	p.T474Pfs*3	2	Low penetrance
APC	c.3920T>A	p.I1307K	3	Low penetrance
FANCC	c.996+1G>A	p.X332_splice	1	Recessive allele
RECQL4	c.2464-1G>C	p.X822_splice	1	Recessive allele
RAD50	c.3277C>T	p.R1093*	1	Uncertain clinical actionability

Raj N, et al. JCO Precision Oncology 2018 :2, 1-18

- Germline analysis included 76 genes known to be associated with hereditary cancer predisposition
- Germline genetic analysis identified clinically actionable pathogenic or likely pathogenic variants in 14 of 88 patients (16%), including mutations in high-penetrance cancer susceptibility genes (MEN1, TSC2, and VHL).

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Genetic Testing for Pancreatic Cancer

- Based on previous studies, family history may be contributory
- Given the high frequency of predisposing mutations and the absence of effective predictors of mutations, genetic testing of all patients with pancreatic is likely warrented
- MGT typically performed → other cancer risks, information for family members

Consideration for Screening - 2019 International Cancer of the Pancreas Screening (CAPS) Consortium

- Individuals with a CDKN2A or STK11 mutation regardless of family history, initiate at age 40
- Individuals with a BRCA2 mutation with ≥1 FDR or ≥2 relatives with PC, initiate by age 45-50
- Individuals with ATM, PALB2, BRCA1, Lynch mutation and ≥1 FDR with PC, initiate by age 45-50
- Individuals with PRSS1or other hereditary pancreatitis mutation with a clinical history of pancreatitis , initiate 20 years after onset of symptoms of age 40
- Individuals who have at least one first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer (familial pancreatic cancer kindred), initiate by age 50-55

Brand, et al. Gut 2007

Screening for Pancreatic Cancer - CAPS

- Annual Endoscopic ultrasound
- Annual MRI/MRCP

Consideration for Screening – NCCN High-Risk Assessment: Breast, Ovarian and Pancreatic Cancer Guidelines Version 3.2025

- Individuals with a CDKN2A mutation regardless of family history, initiate at age 40
- Individuals with a STK11 mutation regardless of family history, initiate at age 30-35
- *Individuals with an ATM or BRCA2 mutation regardless of family history, initiate at age 50*
- Individuals with BRCA1, MLH1, MSH2, MSH2, EPCAM, PALB2 or TP53 mutation and ≥1 FDR or SDR with PC, initiate at age 50
- Individuals with PRSS1 or other hereditary pancreatitis mutation with a clinical history of pancreatitis , initiate 20 years after onset of symptoms of age 40
- A family history of pancreatic cancer in ≥1 first-degree and ≥1 second-degree relatives from the same side of the family

Screening for Pancreatic Cancer - NCCN

- Annual contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS)
  - Shorter screening intervals, based on clinical judgment

Germline Mutations and Treatment for Pancreatic Cancer

- Increased survival for PDAC patients with germline mutations in BRCA1/2 or PALB2 who received platinum chemotherapy.

- Evaluating PARP inhibitors in PDAC patients with germline mutations in BRCA1/2

- Immune checkpoint inhibitors to treat tumors with microsatellite instability or mismatch repair deficiency

Key points

- All patients with pancreatic adenocarcinoma meet NCCN guidelines for consideration of genetic testing
- Germline genetic testing may aid in treatment decision making for the patients and determine future caner surveillance
- Testing may provide additional information to family members with respect to cancer risk and screening

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Questions ?