# Genetics of Pancreatic Cancer

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Pancreatic Cancer Action Network
Educational Seminar
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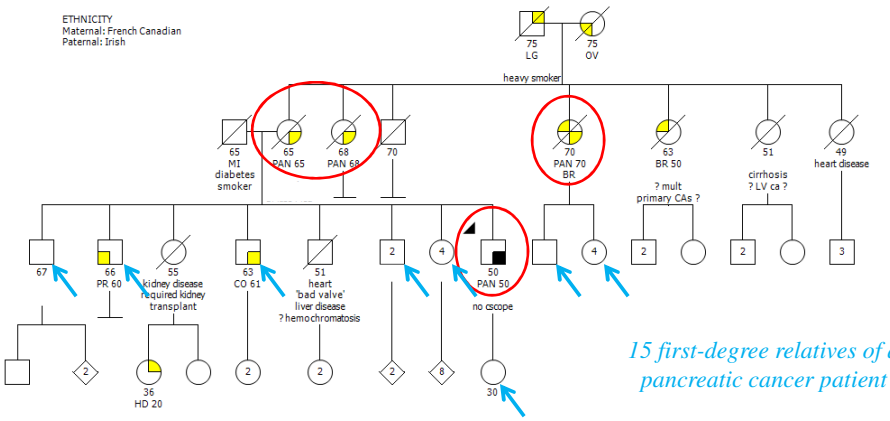
## Disclosures

- No relevant disclosures or conflicts of interest to report

# Objectives

- Review basic concepts of genetics and how they apply to understanding pancreatic cancer risks
- Discuss current understanding of hereditary/genetic syndromes associated with pancreatic cancer risk
- Discuss current understanding of "familial pancreatic cancer," (families with "too much" pancreatic cancer)
- Review the evolving data on strategies to screen for pancreatic cancer in high-risk individuals

Some families have inherited risks of pancreatic cancer




*15 first-degree relatives of a pancreatic cancer patient*

**How can we understand and reduce this family's risk of pancreatic cancer?**

## Understanding and reducing risk

- Identifying high-risk individuals
  - When to consider a genetic predisposition to pancreatic cancer?
  - Families with "too much" pancreatic cancer
- Managing high-risk individuals
  - Can we effectively screen for pancreatic cancer?
  - Other risk-reducing interventions?

## Outline

- Primer on Genetics
- Inherited Risks of Pancreatic Cancer
  - Specific Genetic Syndromes
  - "Familial Pancreatic Cancer"
- Pancreatic Cancer Screening
  - Who?
  - When?
  - How?

# Outline

- Primer on Genetics
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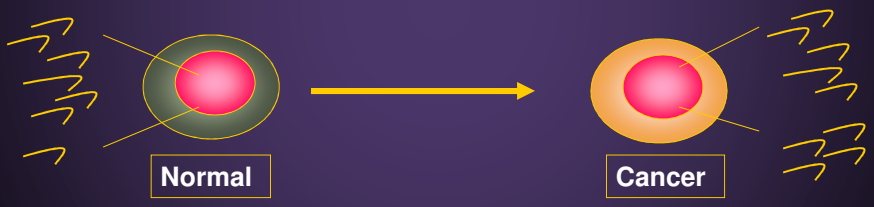
Slide courtesy of Dr. Judy Garber

## Cancer is a Genetic Disease

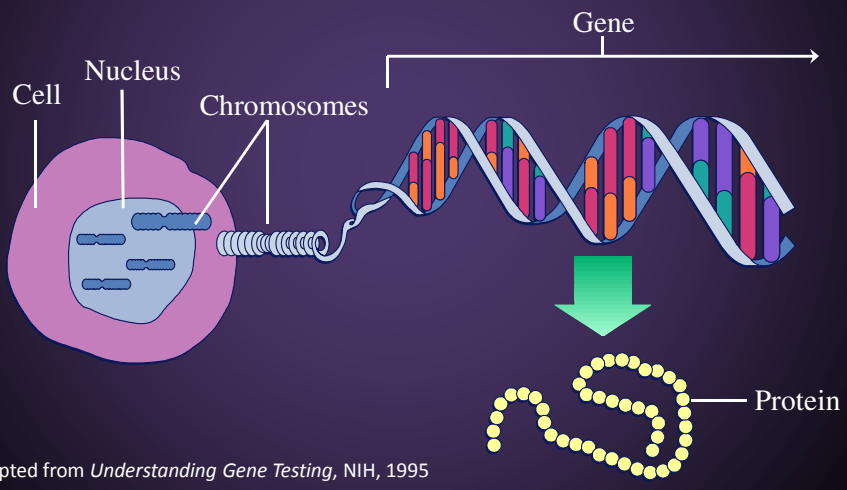
Normal cells and cancer cells contain the same 30,000 genes.

- What distinguishes them is which genes are turned on and off



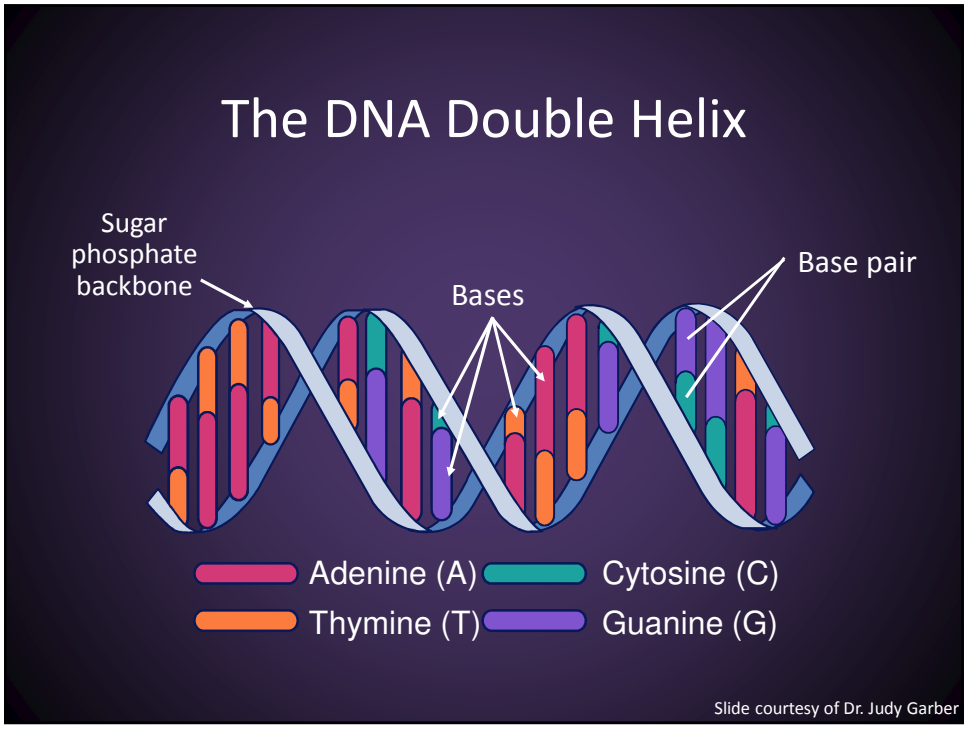

Slide courtesy of Dr. Judy Garber

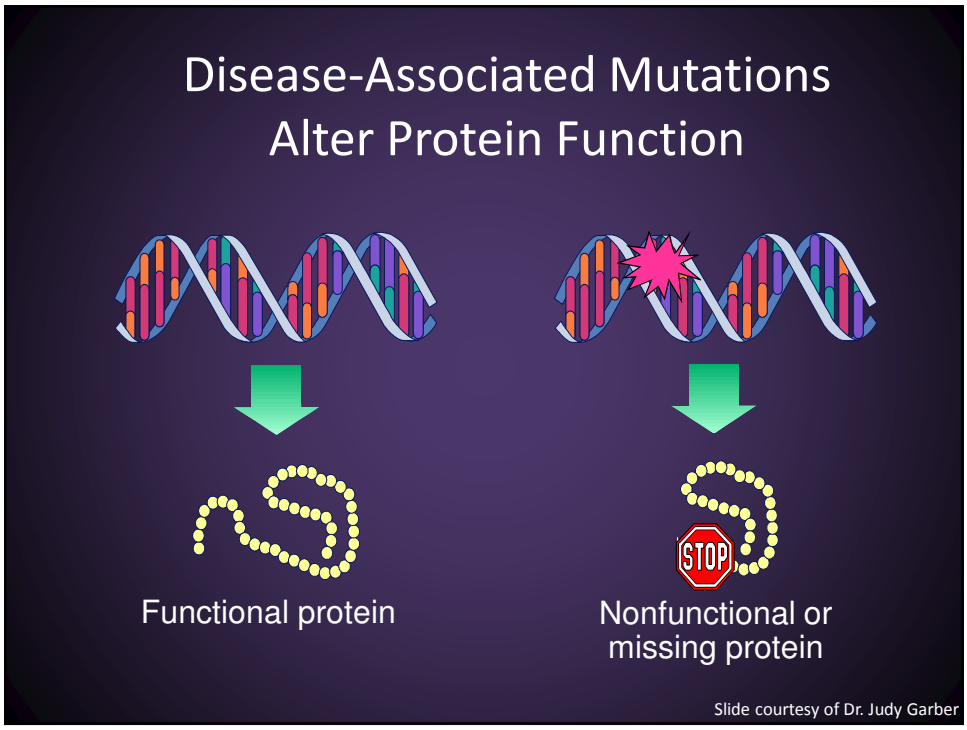
## Chromosomes, DNA, and Genes




Adapted from *Understanding Gene Testing*, NIH, 1995

Slide courtesy of Dr. Judy Garber


The DNA Double Helix
Sugar phosphate backbone
Bases
Base pair
Adenine (A)
Cytosine (C)
Thymine (T)
Guanine (G)
Slide courtesy of Dr. Judy Garber


Disease-Associated Mutations Alter Protein Function
STOP
Functional protein
Nonfunctional or missing protein
Slide courtesy of Dr. Judy Garber

# Genetic Code

A **codon** is made of 3 base pairs

64 codons total

1 codon (AUG) encodes methionine *and* starts translation of all proteins


61 codons encode 20 amino acids (redundant code)


3 codons stop protein translation


Slide courtesy of Dr. Judy Garber

# Examples of Mutation Types

Wild Type (no mutation): The red dog saw the fox and the cat run.

Small Insertion: The red doX gsa wth efo xan dth eca tru n.

Large Insertion: The red dog and the big bat saw the fox and the cat run.

Small Deletion: The red dog sat hef oxa ndt hec atr un.

Large Deletion: The red dog sa

Rearrangement: The red __ fox and the cat run dog saw the.

Duplication: The red dog saw the fox and The red dog the cat run.

Missense: The red dog saw the fAx and the cat run.

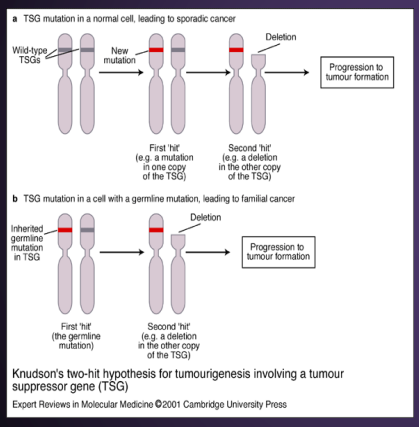
Variant: The red dog saw the fox and the Kat run.

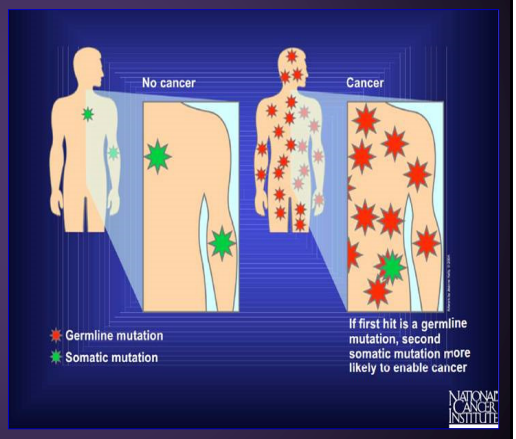
Slide courtesy of Dr. Judy Garber

# Some key terms

- Genotype
  - The genetic makeup of a cell or individual
- Germline mutation
  - A mutation in the patient
  - A mutation in cells that can be passed on to offspring
    - Sperm
    - Oocyte
  - Usually inherited from a parent
  - Present in every cell in the body
- Phenotype
  - The observed traits of a cell or individual
- Somatic mutation
  - A mutation in the tumor
  - Mutations that develop in differentiated/mature cells
  - Not inherited
  - Cannot be passed on to children
  - Only present in cells that acquire the mutation
  - Potential for "targeted" therapies against a specific mutation
    - ? Ability to spare non-cancerous cells

# Knudson Two-Hit Hypothesis



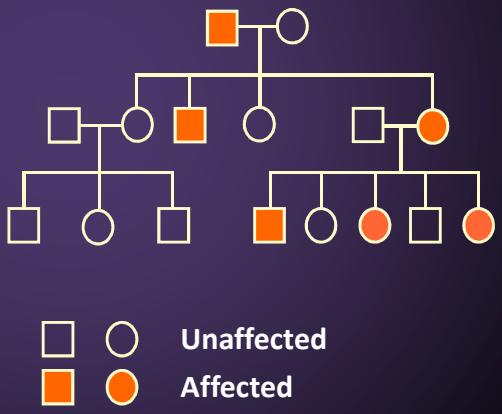




*In patients who inherit a germline mutation, the "first hit" is already present in every cell in their body*

Slide courtesy of Dr. Judy Garber

# Autosomal Dominant Inheritance

- Each child has 50% chance of inheriting the mutation
- No "skipped generations"
- Equally transmitted by men and women




Slide courtesy of Dr. Judy Garber

# Concept of Penetrance

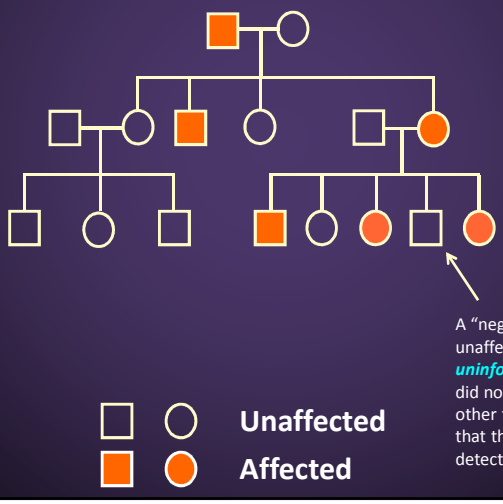
- Inheriting a cancer susceptibility gene does not guarantee the development of cancer
- Reasons for incomplete penetrance?
  - Environmental effects?
  - Other "modifier" genes?

# Why do genetic testing for inherited cancer syndromes?

- Identify other cancers for which the patient may be at risk
- Offer predictive testing to other family members to see who might also be at risk for cancer in the future

# Why test someone who's "affected"?

Helps guide interpretation of "negative" or "variant" test results




A "negative" genetic test result in an unaffected patient is considered ***uninformative*** – it could be that they did not inherit a mutation carried by other family members ***OR*** it could be that there is no mutation that *can* be detected

Once the mutation is found in one person in the family, the rest of the family can be tested to see whether they do or do NOT share the mutation.

Such "single site" testing is considered *truly informative* – you either have it or you don't (also cheaper and quicker).

Slide courtesy of Dr. Judy Garber

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# Hereditary Cancer: Identifying *who is at risk?*

- Breast cancer
  - 10-20% of "triple-negative" breast cancer due to *BRCA1* or *BRCA2* mutations
  - >10% of breast cancers in women of Ashkenazi Jewish descent due to *BRCA1/2* mutations
- Ovarian/Fallopian Tube/Peritoneal cancer
  - 5-15% due to *BRCA1* or *BRCA2* mutations
  - 30-40% of ovarian cancers in women of Ashkenazi Jewish descent due to *BRCA1/2* mutations
- Colorectal cancer
  - 3% due to Lynch syndrome (HNPCC)
  - 1% due to familial polyposis syndromes
- Uterine (endometrial) cancer
  - 2% due to Lynch syndrome (HNPCC)
- Pancreatic cancer
  - ??

# Hereditary Cancer: How to *manage and reduce risk?*

- Breast cancer
  - Early-onset breast screening: mammography, ultrasound, MRI
  - Risk-reducing prophylactic mastectomy
- Ovarian/Fallopian Tube/Peritoneal cancer
  - Screening is likely ineffective
  - Risk-reducing prophylactic salpingo-oophorectomy at the completion of childbirth
- Colorectal cancer
  - Annual colonoscopies
  - Consideration of risk-reducing prophylactic colectomy for some patients
- Uterine (endometrial) cancer
  - Risk-reducing prophylactic hysterectomy at the completion of childbirth
- Pancreatic cancer
  - ??

# Defining Inherited Risks of Pancreatic Cancer

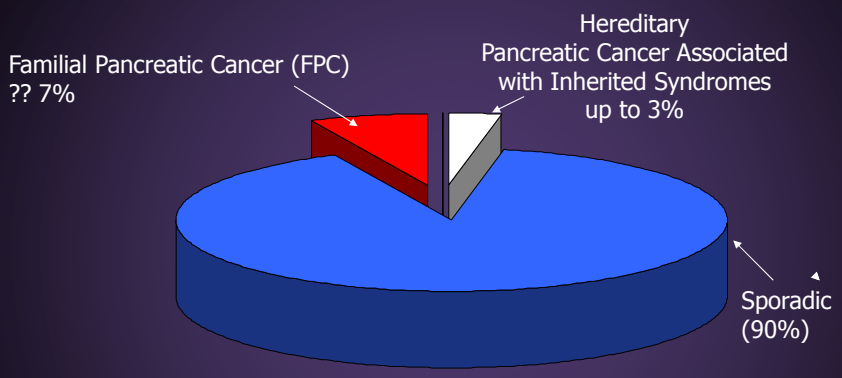
**Hereditary Pancreatic Cancer Risk**

- Having a known genetic syndrome/mutation that increased pancreatic cancer risk
- Other associated cancer risks, depending on specific syndrome/mutation

**Familial Pancreatic Cancer (FPC)**

- A term used to describe families with "too much" pancreatic cancer
  - WITHOUT an identifiable genetic syndrome/mutation

# Hereditary Susceptibility to Pancreatic Cancer




- Up to 10% of all pancreatic cancers occur in patients with a family history of pancreatic cancer
- Having a first degree relative with pancreatic cancer increases risk of disease

# Defining Inherited Risks of Pancreatic Cancer

**Hereditary Pancreatic Cancer Risk**

- Having a known genetic syndrome/mutation that increased pancreatic cancer risk
- Other associated cancer risks, depending on specific syndrome/mutation

**Familial Pancreatic Cancer (FPC)**

- A term used to describe families with "too much" pancreatic cancer
  - WITHOUT an identifiable genetic syndrome/mutation

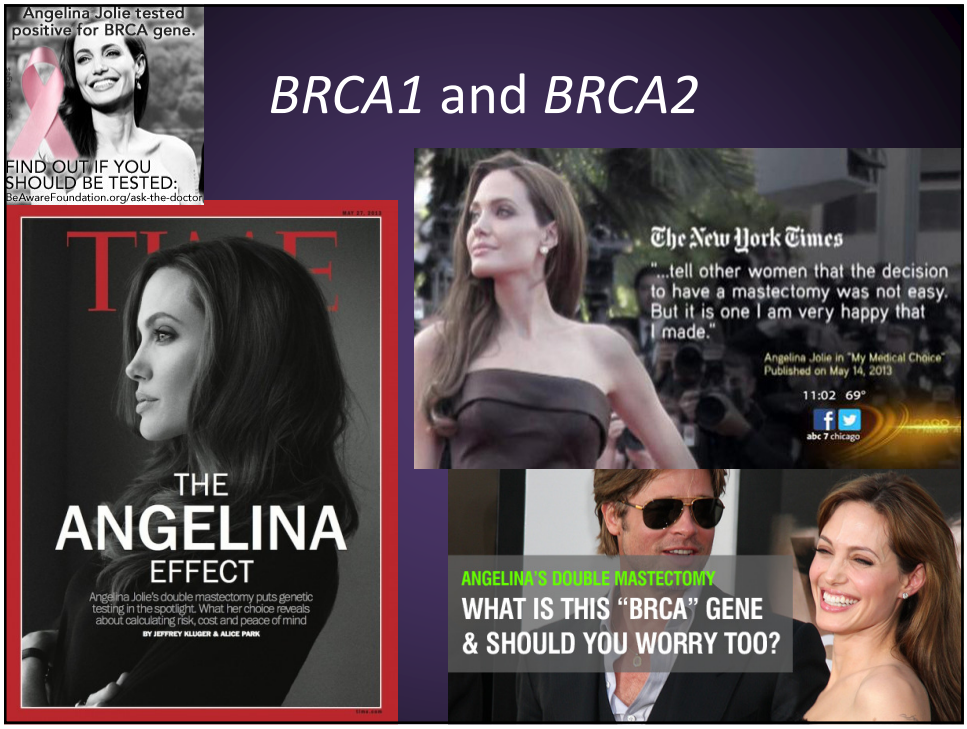
# Identifiable Genetic Syndromes with Increased Pancreatic Cancer Risk

**Not so rare…**

- Hereditary breast/ovarian cancer (HBOC)
  - *BRCA1* and *BRCA2* genes
- Lynch syndrome (hereditary nonpolyposis colorectal cancer; HNPCC)
  - DNA mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*
- Other gene(s)?
  - *ATM*

**Rare**

- Peutz-Jeghers syndrome (PJS)
  - *STK11*
- Li-Fraumeni syndrome (LFS)
  - *TP53* gene
- Familial multiple mole melanoma (FAMMM) syndrome
  - *CDKN2A* (p16) gene
- Hereditary pancreatitis
  - *PRSS1* (cationic trypsinogen) gene
- Other gene(s)?
  - *PALB2*




# *BRCA1* and *BRCA2*

- Most common hereditary breast and ovarian cancer syndrome
  - ~60% lifetime risk of female breast cancer
  - ~20-40% lifetime risk of ovarian cancer

  *Overall risks of cancer in <u>males</u> are much lower, so <u>family histories can be subtle</u>*
- Roughly 2.5% of population with Ashkenazi Jewish heritage have *BRCA1/2* mutations
- Thought to be most common identifiable genes underlying pancreatic cancer risk
  - *<u>Not</u>* early-onset pancreatic cancer
    - *Can be very difficult to get insurance coverage for BRCA1/2 testing in pancreatic cancer patients who are older and/or men*

# Lynch syndrome (HNPCC)

- Most common hereditary GI cancer syndrome
  - 3% of all colorectal cancers
    - 20-80% lifetime risk of colorectal cancer
  - 2% of all uterine cancers
    - 20-60% lifetime risk of uterine cancer
- Typically, young onset cancers
  - Median age of diagnosis ~45

# Aldred Scott Warthin, M.D., Ph.D.

- University of Michigan pathologist, 1895

"His seamstress was depressed because she was convinced, based on her family history, that she would one day die of cancer of the female organs or bowels… [She] told Warthin that it was inevitable that she would die early in life because 'Everyone in my family dies of those cancers.' "

→ She later died at age 55 (1901) of metastatic endometrial cancer

→ Warthin published a description of this "Family G" in 1913.

Douglas JA. *JAMA* 2005;294:2195-2202.
Lynch HT and JF Lynch. *Dis Markers* 2004;20:181-98.

# Lynch Syndrome Cancer Spectrum

| Cancer Type | Lifetime Risk | Comment |
|---|---|---|
| Colorectal cancer | 28-75% | Risk may be lower in *MSH6* and *PMS2* mutation carriers. |
| Endometrial cancer | 27-60% | Usually endometrioid histology |
| Ovarian cancer | 6-20% | Usually endometrioid histology |
| Gastric cancer | <1-6% | May be more common in Asian patients and those with MLH1 mutations |
| Urothelial cancers | 8-12% | More common in MSH2 mutation carriers |
| Sebaceous neoplasms and keratoacanthomas | Varies, depending on family | "Muir-Torre" variant; usually only seen in MLH1 or MSH2 mutation carriers |
| Small bowel carcinomas | ~4% | |
| **Pancreatic cancer (exocrine)** | **3-4%** | |
| Biliary carcinomas | <1-4% | |
| CNS tumors | <1-2% | "Turcot" variant; mostly gliomas |
| Breast cancer | ? | |
| Prostate cancer | ? | |


Barrow E, et al. *Clin Genet* 2009;75:141-9.
Bauer CM, et al. *Fam Cancer* 2011;10:37-42.
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Buerki N, et al. *Genes Chromosomes Cancer* 2012;51:83-91.
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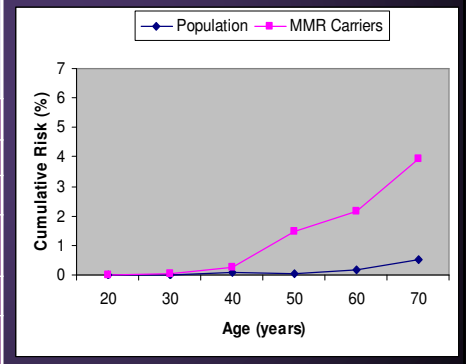
van der Post RS, et al. *J Med Genet* 2010;47:464-70.
Walsh MD, et al. *Clin Cancer Res* 2010;16:2214-24.


# Risk of Pancreatic Cancer in Families With Lynch Syndrome

JAMA. 2009;302(16):1790-1795

Fay Kastrinos, MD, MPH, Bhramar Mukherjee, PhD, Nabihah Tayob, MS, Fei Wang, MS, Jennifer Sparr, MD, Victoria M. Raymond, MS, Prathap Bandipalliam, MD, Elena M. Stoffel, MD, MPH, Stephen B. Gruber, MD, MPH, Sapna Syngal, MD, MPH

| Age* | Cumulative Risk Population† % | Cumulative Risk Lynch Carriers % (95% CI) |
|---|---|---|
| 20 | 0 | 0 |
| 30 | 0.00 | 0.04 |
| 40 | 0.01 | 0.26 |
| 50 | 0.04 | 1.46 (0.56, 3.22) |
| 60 | 0.18 | 2.16 |
| **70** | **0.52** | **3.95 (1.52, 6.63)** |




†Surveillance Epidemiology and End Results 2001-2005

# Other Cancer Risks for Families With Lynch Syndrome

| Cancer | Observed No. | Expected No. | SIR* | 95% CI | *P* |
|---|---|---|---|---|---|
| Lynch Carriers | | | | | |
| Colorectal cancer | 16 | 0.78 | 20.48 | 11.71 to 33.27 | <.001 |
| Endometrial cancer | 6 | 0.20 | 30.62 | 11.24 to 66.64 | <.001 |
| Ovary cancer | 3 | 0.16 | 18.81 | 3.88 to 54.95 | <.001 |
| Renal cancer | 3 | 0.27 | 11.22 | 2.31 to 32.79 | <.001 |
| **Pancreas cancer** | 2 | 0.19 | ***10.68*** | **2.68 to 47.70** | **.001** |
| Gastric cancer | 2 | 0.20 | 9.78 | 1.18 to 35.30 | .009 |
| Urinary bladder cancer | 2 | 0.21 | 9.51 | 1.15 to 34.37 | .009 |
| Breast cancer | 7 | 1.77 | 3.95 | 1.59 to 8.13 | .001 |
| Prostate cancer | 3 | 1.21 | 2.49 | 0.51 to 7.27 | .18 |
| Noncarriers | | | | | |
| Colorectal cancer | 5 | 4.88 | 1.02 | 0.33 to 2.39 | .97 |
| Lung cancer | 3 | 4.68 | 0.64 | 0.13 to 1.87 | .51 |
| Breast cancer | 5 | 6.95 | 0.72 | 0.23 to 1.68 | .52 |
| Prostate cancer | 9 | 5.53 | 1.63 | 0.74 to 3.09 | .18 |

*Age-, Sex-, and Country-Specific SIRs for Carriers & Noncarriers Compared With the General Population

Win AK, et al. *J Clin Oncol* 2012; 30:958-64

# Rare syndromes

- Peutz-Jeghers syndrome (PJS) – *STK11* gene
  - Lip freckling and small intestine polyps early in life
  - Breast cancer, colon cancer risks
  - Markedly elevated pancreatic cancer risk
- Li-Fraumeni syndrome (LFS) – *TP53* gene
  - Risk of multiple lifetime cancers (>90% lifetime risk of any cancer)
    - Early breast cancer, sarcomas, leukemias/lymphomas, adrenal cancers
    - Gastric, colorectal, lung cancers
  - Association with pancreatic cancer, but frequency unclear
- Familial multiple mole/melanoma (FAMMM) syndrome – *CDKN2A* (p16) gene
  - Most commonly, atypical moles and melanomas are the predominant finding
  - Increased risk of pancreatic cancer; frequency unclear
- Hereditary pancreatitis – *PRSS1* gene
  - Early-onset recurrent pancreatitis
  - Elevated pancreatic cancer risk (? Related to risk of pancreatitis)

## Known Genetic Syndromes Associated with Increased Pancreatic Cancer Risk

| Syndrome | Culprit gene(s) | Pancreatic cancer risk |
|---|---|---|
| Hereditary breast cancer | Fanconi anemia pathway genes (*BRCA1*, *BRCA2*, *PALB2*) | Up to 6-fold increased risk |
| Lynch syndrome | DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*) | 8-10-fold increased lifetime risk |
| Peutz-Jeghers syndrome | *STK11* | Up to 132-fold increased lifetime risk |
| Hereditary pancreatitis | *PRSS1* (cationic trypsinogen gene) | Up to 60-fold increased risk |
| Familial multiple mole and melanoma (FAMMM) syndrome | *CDKN2A/p16* | Up to 13-fold increased lifetime risk |
| Li-Fraumeni syndrome | *TP53* | ?? |
| Ataxia-telangiectasia | *ATM* | ?? |

Kastrinos F, et al. *JAMA* 2009;302:1790-5.
Roberts NJ, et al. *Cancer Discov* 2012;2:41-6.
Canto MI, et al. *Gastroenterology* 2012;142:796-804.

## When to do genetic testing?

- Minimal guidelines to help with this
  - Guidelines for *BRCA1/2* testing, Lynch testing, etc, mention pancreatic cancer risks, but pancreatic cancer is far from the focus of these guidelines
- Insurance often doesn't cover genetic testing for patients with pancreatic cancer, if they don't meet other criteria

# Defining Inherited Risks of Pancreatic Cancer

**Hereditary Pancreatic Cancer Risk**

- Having a known genetic syndrome/mutation that increased pancreatic cancer risk
- Other associated cancer risks, depending on specific syndrome/mutation

**Familial Pancreatic Cancer (FPC)**

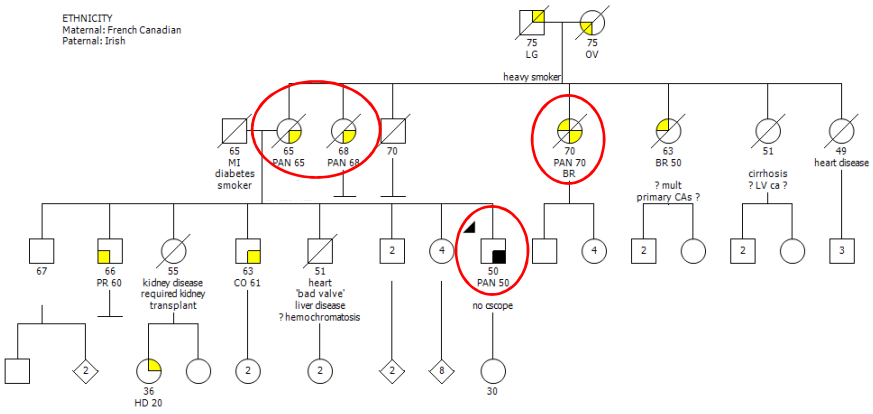
- A term used to describe families with "too much" pancreatic cancer
  - WITHOUT an identifiable genetic syndrome/mutation

# Familial Pancreatic Cancer (FPC)

- A term used to describe families (not individuals)
- Families with at least a pair of first-degree relatives (FDRs) with pancreatic cancer

## Familial pancreatic cancer (FPC)

Families with at least a pair of first-degree relatives (FDRs) with pancreatic cancer

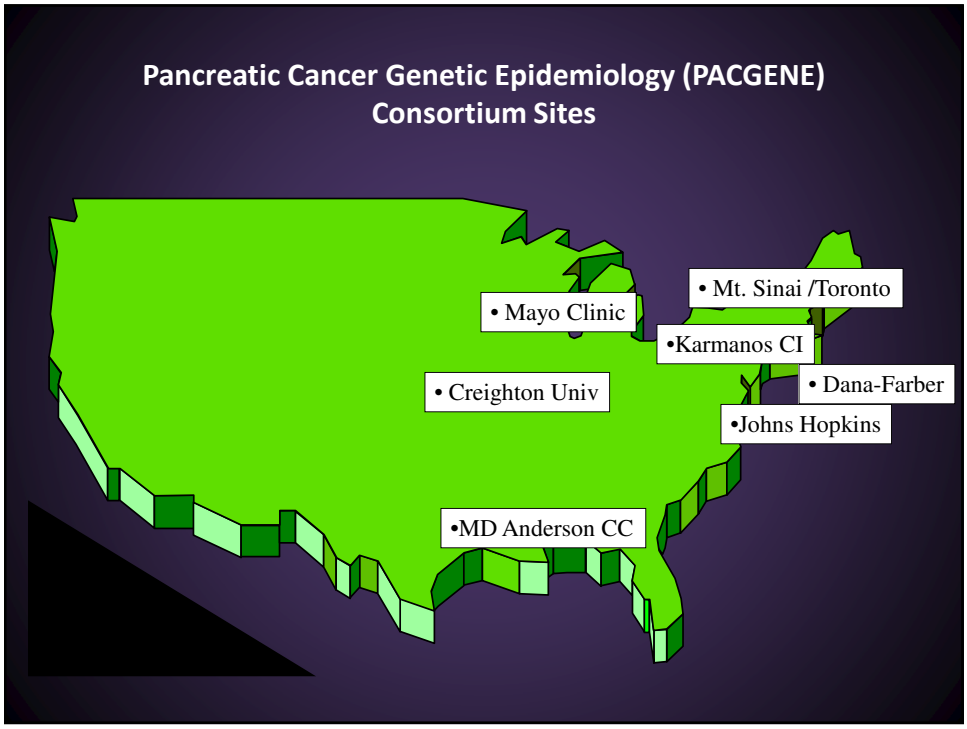



# Within FPC families…

**Median age of pancreatic cancer diagnoses within FPC families is ~65 years old**

| | Standard incidence ratio (95% CI) | Lifetime risk | Incidence per 100,000 |
|---|---|---|---|
| ≥3 FDRs with pancreatic cancer | 32 (10.4-74.7) | ~40% | 288 |
| 2 FDRs with pancreatic cancer | 6.4 (1.8-16.4) | 8-12% | 58 |
| 1 FDR with pancreatic cancer | 4.5 (0.54-16.3) | 6.0% | 41 |
| General population | 1 | 1.3% | 9 |

Adapted from:
Klein AP, et al. *Cancer Res* 2004;64:2634-8.
Grover S and S Syngal. *Gastroenterology* 2010;139:1076-80.

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## Reasons to Screen High Risk Individuals

- Surgical options exist for early pancreatic neoplasia
- Currently, >80% of pancreatic cancer diagnosed at advanced stages
- We know how to identify (at least some) individuals at high risk of pancreatic cancer

## Reasons Not to Screen

- Currently, *no data on survival benefit* from screening and treatment of asymptomatic high-risk individuals
- Low sensitivity of some screening modalities
- False positives may lead to unnecessary surgery/biopsies
- High incidence of chronic pancreatitis changes in high-risk individuals
- Quality of life in patients undergoing screening
- Cost-effectiveness of different screening strategies remains to be determined

# Pancreatic Cancer Screening

- Does it work?
- Who to screen?
- When to screen?
- How to screen?
- Potential downsides to screening?

International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer

Marcia Irene Canto,[1] Femme Harinck,[2] Ralph H Hruban,[3] George Johan Offerhaus,[4] Jan-Werner Poley,[2] Ihab Kamel,[5] Yung Nio,[6] Richard S Schulick,[7] Claudio Bassi,[8] Irma Kluijt,[9] Michael J Levy,[10] Amitabh Chak,[11] Paul Fockens,[12] Michael Goggins,[1] Marco Bruno,[2] on behalf of the International Cancer of the Pancreas Screening (CAPS) Consortium

**2013 CAPS Consortium Statements – Key questions:**

- Who should be screened for pancreatic cancer?
- How should pancreatic cancer screening and follow up be done?
- When should pancreatic surgery be considered?
- What are the goals of screening? What outcome(s) should be considered a success?

Canto et al. *Gut* 2013;62:339-47.

## CAPS Consortium: Who should be screened?

- >5% lifetime risk, based on family history (FPC)
  - 3 or more family members with pancreatic cancer, if 1 is a first-degree relative
  - 2 or more first-degree relatives with pancreatic cancer
- >5% lifetime risk, based on genetic status
  - All patients with Peutz-Jeghers syndrome
  - BRCA, FAMMM, Lynch syndrome or PALB2 mutation carriers with 1 first-degree relative with pancreatic cancer
  - BRCA mutation carriers with 2 non-first-degree relatives with pancreatic cancer

Canto et al. *Gut* 2013;62:339-47.

## Pancreatic Cancer – How to Screen?

- CT scans?
- MRI/MRCP?
- Endoscopic ultrasound (EUS)?

## Imaging Can Detect Pancreatic Cancer/Precursor Lesions: *CT Scan*

- Advantages
  - Low cost
  - Wide availability
  - Standard procedures
  - Can detect large lesions
- Disadvantages
  - Limited sensitivity, esp for smaller lesions
  - Radiation exposure
  - Allergic reactions and kidney damage from IV contrast

## Imaging Can Detect Pancreatic Cancer/Precursor Lesions: *MRI/MRCP*

Advantages:

- High diagnostic accuracy (80-100% for main and side branch IPMN)
- No radiation
- Not operator dependant

Disadvantages:

- High cost
- Cannot accurately detect PanIN (pre-invasive) lesions in side branches
- Contraindicated in patients with metallic implants
- Claustrophobia

## Imaging Can Detect Pancreatic Cancer/Precursor Lesions: ***EUS***

Advantages
- No exposure to radiation
- Provides high-resolution images
- High diagnostic accuracy for cystic lesions (90%)
- Better visualization of parenchymal abnormalities

Disadvantages
- High cost
- Not widely available
- High inter-observer variability
- Risk associated with sedation and endoscopy

## Pancreatic Cancer Screening

- 216 "high-risk" patients
  - 195 with FPC
  - 21 with *BRCA2* mutations and a family history of pancreatic cancer
- Screening with CT, MRCP, and EUS
  - CT scanning had much lower sensitivity than MRCP and EUS

Canto et al. *Gastroenterology* 2012;142:796-804.

# Pancreatic Cancer Screening

- 42% of patients (92/216) had focal pancreatic lesion
  - Most commonly cysts (IPMNs)
    - 60% of patients with cysts had multiple cysts
- Incidence of abnormalities increased with age
  - 14% of subjects age <50
  - 53% of subjects age 60-69
- 5 patients went on to surgical resection of part/all of the pancreas
  - All had evidence of pre-invasive neoplasia
  - No invasive adenocarcinomas

Canto et al. *Gastroenterology* 2012;142:796-804.

# CAPS Consortium: How to screen? When to operate?

- Initial screening with MRI/MRCP and/or endoscopic ultrasound (EUS)
- Surgical consideration for "high-risk" lesions
  - Definition of "high-risk" is unclear

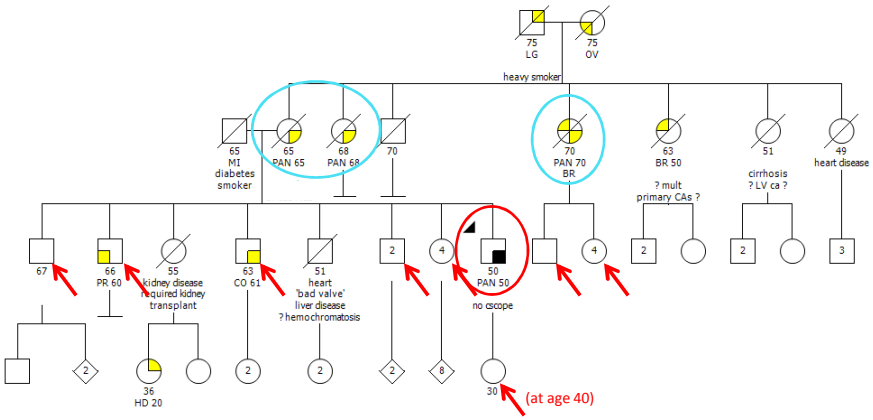
Canto et al. *Gut* 2013;62:339-47.

# Downsides to screening?

- Very different scenario than other types of cancer screening/surveillance
  - Removing a colon polyp is not the same as pancreatic resection
  - Patients are anxious – no need to convince to get screened
  - Challenge will be not to over-screen
  - High rate of non-malignant lesions
  - Major risks: unnecessary intervention, anxiety

# Pancreatic Cancer Screening

- Does it work?
  - Not yet proven…… we hope it works!
  - IF screening works, it is most likely to be effective in high-risk individuals
- Who to screen?
  >5% lifetime risk based on family history and/or genetic status
  - Within FPC families, anyone who is a first-degree relative of someone with pancreatic cancer
  - Mutation carriers (*BRCA1/2*, Lynch, other syndromes) with pancreatic cancer in family
  - All patients with Peutz-Jeghers syndrome and hereditary pancreatitis (both rare)
- When to screen?
  - Age ≥50 (or 10 years younger than youngest diagnosis in family)
  - Age 30-35 in Peutz-Jeghers syndrome
- How to screen?
  - Annual screening, alternating MRI and endoscopic ultrasound (EUS)
  - Increased surveillance and aggressive management of IPMNs and other suspected lesions
  - At specialized centers (ideally under research protocols)
- Potential downsides to screening?
  - Anxiety related to pancreatic abnormalities/cysts
  - Additional testing procedures for cysts or incidental findings




**WHO in this family should we be screening pancreatic cancer ?**

# Summary

- Pancreatic cancer is often a familial/genetic disease
  - Most families with "too much" pancreatic cancer (FPC) will not have an identifiable genetic syndrome
- Identification of specific genetic syndromes requires ability to recognize family history patterns (*and convincing insurance companies to pay for testing*)
  - *BRCA1/2*
  - Lynch syndrome
- Pancreatic cancer screening should be considered for high-risk individuals
  - Need to emphasize limitations/risks, and the absence of data about the effectiveness of screening
- A deeper understanding of these issues is needed to get us to the point of being able to effectively prevent pancreatic cancer

# Questions?

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