

Genetics & Prevention of Pancreatic Cancer

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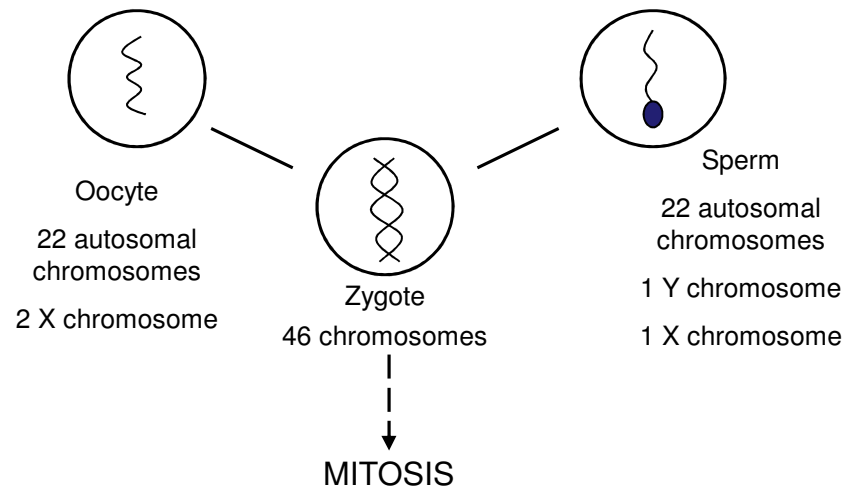
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Overview

- Background: what are genes?
- Risk factors for pancreatic cancer
- What does this mean for family members?

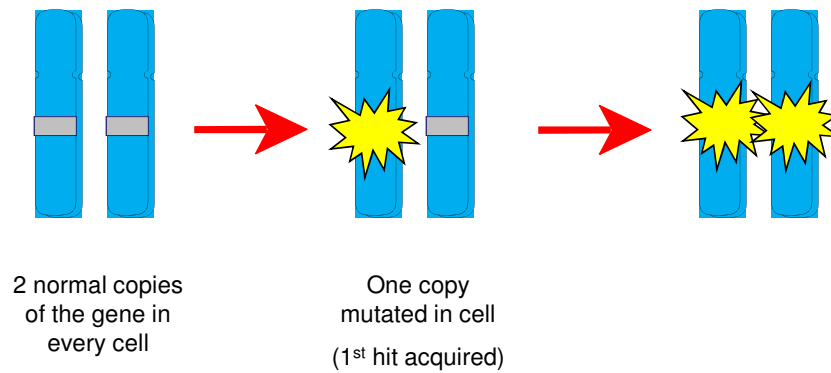
Genetics - Human Cell Formation



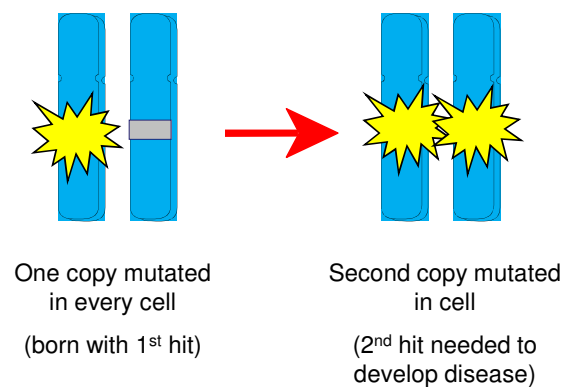
Two Kinds of Gene Mutations

- Somatic Mutations → Sporadic Cancer
- Germ Line Mutations → Inherited Syndrome

Somatic Mutations (Sporadic Disease)



Germline Mutation (Inherited Disease)



Incidence of Pancreatic Cancer by Number of Affected First Degree Relatives

10-15% of patients with pancreatic cancer have a familial aggregation or an inherited predisposition

Number of FDRs	Standardized Incidence Ratio	Incidence (per 100,000 in the US Population)
General U.S. (reference)	-	9
1	4.5 x	41
2	6.4 x	58
3 or more	32.0 x	288

Klein AP et al. Cancer Research 2004; 64: 2634-2638

Smoking...

is the major known risk factor for this cancer

- ▶ associated with ~ 30% of all cases
- ▶ results in **accelerated** tumor progression

Incidence Ratios for Pancreatic Cancer by Cigarette Smoking Status for Those with At Least One First-Degree Relative (FDR) with Pancreatic Cancer

	Standardized Incidence Ratio (95% Confidence Intervals)
Smokers	19.2 (7.7 – 39.5)
Non Smokers	6.25 (1.70 – 16.0)

Klein AP et al. Cancer Research 2004; 64; 2634-2638

Other risk factors...

Risk Factors	Relative Risk
Chronic Pancreatitis	13
Red Meat (men)	1.29
Processed Meat (men and women)	1.19
Obesity (BMI>40)	1.49 (men), 2.76 (women)
Diabetes	1.8-2.0
Alcohol (≥ 3 drinks/day)	1.22
Cholecystectomy	1.23
Partial Gastrectomy	1.54

Raimondi et al. Best Pract Res Clin Gastro 2010; Larsson et al. Br J Cancer 2012; Calle et al. NEJM 2003; Stevens et al. Br J Cancer 2007; Huxley et al. Br J Cancer 2005. Tramacere et al. Int J Cancer 2010. Gong, Zhou et al 2012.

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Inherited Syndromes Predisposing to Pancreatic Cancer

	Gene	Increased Risk
Breast + Ovarian Cancer	BRCA1, BRCA2	2-10
FAMMM	CDKN2A/p16	15-65
Peutz-Jeghers Syndrome	STK11/LKB1	130
Lynch Syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	8
Hereditary pancreatitis	PRSS1/SPINK1	69
Other	PALB2, ATM	?

Familial Pancreatic Cancer

-
- Families with at least two first-degree relatives who have been diagnosed with pancreatic cancer

Breast and Ovarian Cancer Syndrome (BRCA)

- Breast Cancer
- Ovarian Cancer
- Prostate Cancer
- Pancreas Cancer

- Germline Mutation: BRCA 2, BRCA 1

Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)

- Multiple
 - Nevi
 - Dysplastic Nevi
 - Melanomas

- Pancreas Cancer
- Head and Neck: Squamous Cell Cancer
- Germline Mutation: CDKN2A (p16)

Vinarsky et al., Head and Neck 2009

Peutz-Jeghers Syndrome

- ▶ Hamartomatous GI Polyps
- ▶ Mucocutaneous Pigmentation
- ▶ Lifetime Pancreas Cancer Risk ~36%
- ▶ Germline Mutation: STK11

Hereditary Pancreatitis

- ▶ Severe episodes of pancreatitis beginning at a young age (14 yrs)
- ▶ ~40% will develop pancreas cancer
- ▶ Prophylactic total pancreatectomy is considered as pancreas is non-functional
- ▶ Germline mutation: PRSS1 (cationic trypsinogen gene) / SPINK1

Lynch Syndrome (Hereditary Non-Polyposis Colon Cancer Syndrome)

• Colon	63%	
• Endometrium	8%	(28% Women)
• Gastric	6%	
• Pancreaticobiliary	4%	
• Genitourinary	2%	
• Ovary	1%	(3% Women)
• Small Bowel	1%	
• Brain (glioblastoma)		
• Skin (sebaceous)		

*Can we prevent patients
from developing pancreatic
cancer?*

(Or catch it at a treatable phase?)

Pancreatic Intraepithelial Neoplasia (PanIN)

- ▶ Small intraductal lesions formed by abnormal proliferation of ducts
- ▶ Pan-IN demonstrate varying degrees of dysplasia
 - PanIN-1, PanIN-2, and PanIN-3
- ▶ Some pancreatic cancers arise from PanIN, but not all PanIN become cancers
- ▶ Unable to visualize clearly on imaging

Maitra et al. Mod Path 2003.
Terhune et al. CEBP 1998.

Mucinous Cystic Neoplasms & Intraductal Papillary Mucinous Neoplasms

Mucinous Cystic Neoplasm (MCN)

- ▶ Ovarian stroma, possibly arising from ovarian rests within pancreas
- ▶ Invasive carcinoma 6-36%

Intraductal Papillary Mucinous Neoplasm (IPMN)

- ▶ Branch duct vs main duct
 - Different risk of malignancy
 - Branch Duct: ~25%
 - Main Duct: ~70%

Tanaka et al. Pancreatology 2006

Pancreas Cancer Screening Options

Endoscopic Ultrasound (EUS)

- Requires sedation
- Invasive procedure
- Ability to biopsy abnormalities

Magnetic Resonance Imaging (MRI)

- Non-invasive
- Unable to biopsy
- Patient tolerance

Can we incorporate genetic testing into risk stratification?

High-risk program

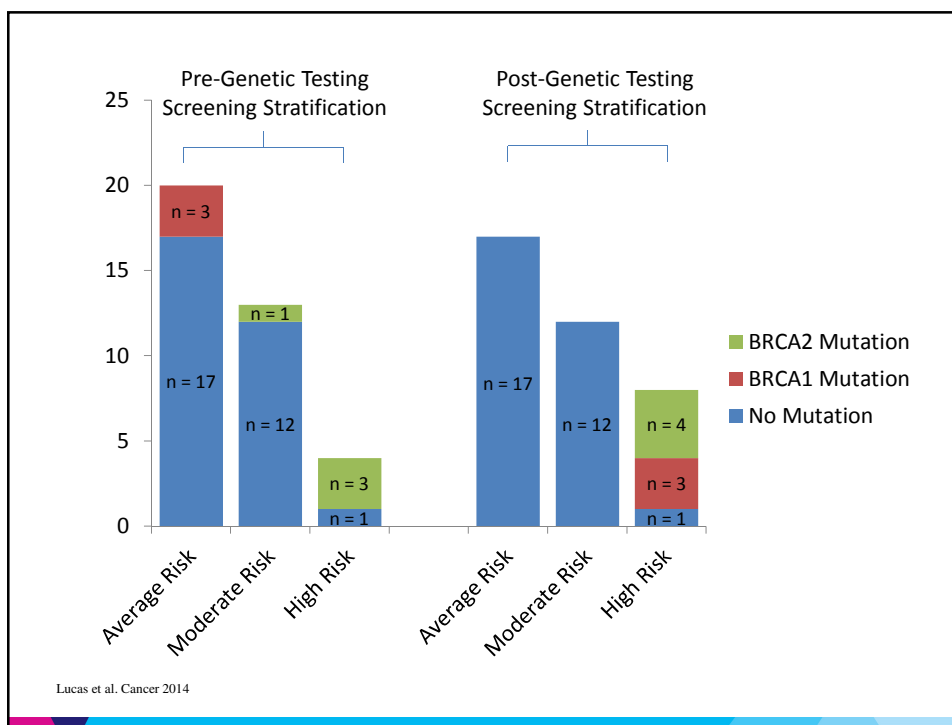
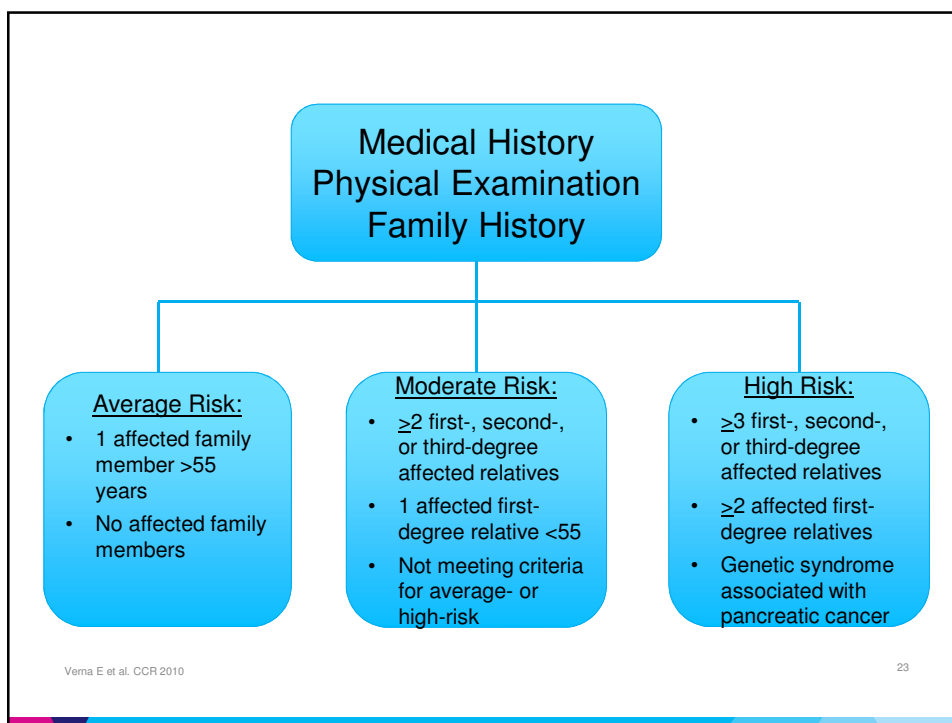
- Unaffected individuals with family history of cancers
- Affected individuals with family history of cancers, young age onset of cancer

Family History Is Important!

- 3 generation family tree
- Asked questions about cancers in the family

Incorporated family history and genetic testing into risk stratification

Lucas et al. Cancer 2014



Can we incorporate genetic testing into risk stratification?

37 unaffected individuals

- 7/37 (18.9%) had gene mutations

32 affected individuals

- 7/32 (21.9%) had gene mutations

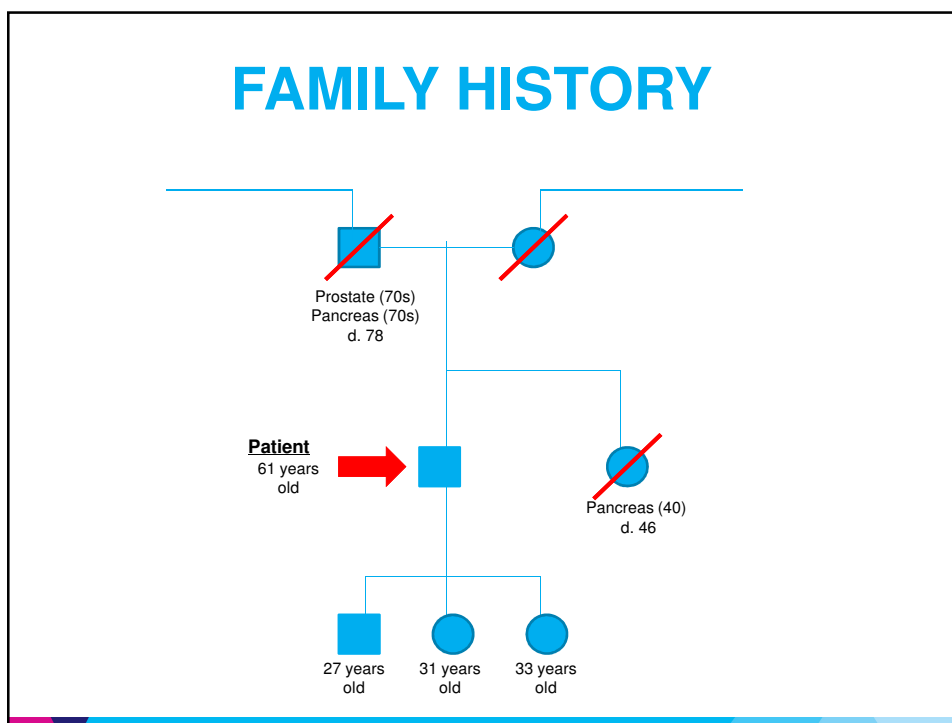
*Large number of Ashkenazi Jewish individuals

Lucas et al. Cancer 2014

PATIENT PRESENTATION - 1

- Sex: Male
- Age: 61
- Ashkenazi Jewish: Yes
- Cigarette Use: Discontinued (minimal use in past)
- Alcohol Use: Occasional
- Diabetes Mellitus: No
- Pancreatitis: No
- Cancer Hx: None
- Past Medical Hx: None
- **Physical Exam**
 - Normal
- **Laboratory Exam**
 - Normal, except CA 19-9

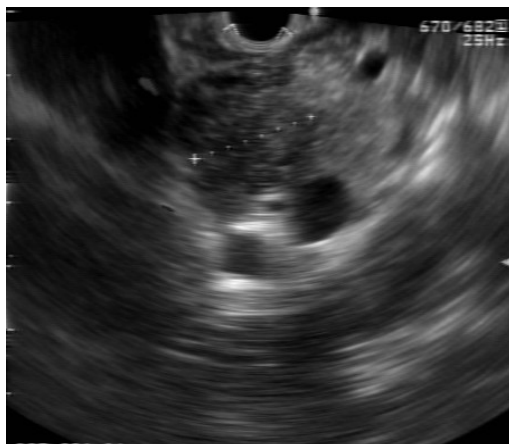
FAMILY HISTORY

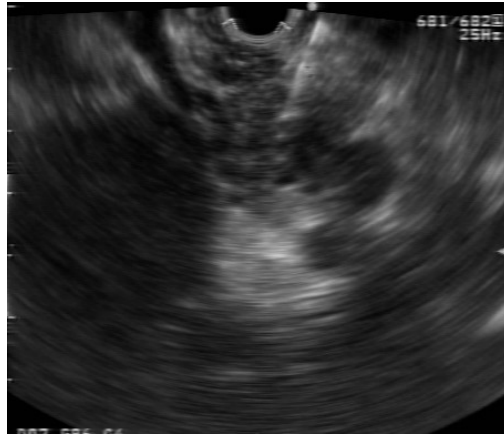


RECOMMENDATIONS

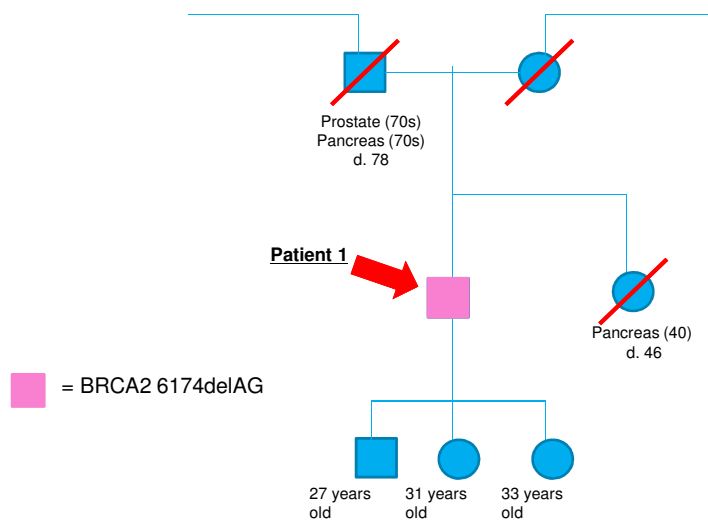
- EUS
- MRI
- Genetic testing

Endoscopic Ultrasound





GENETIC TESTING



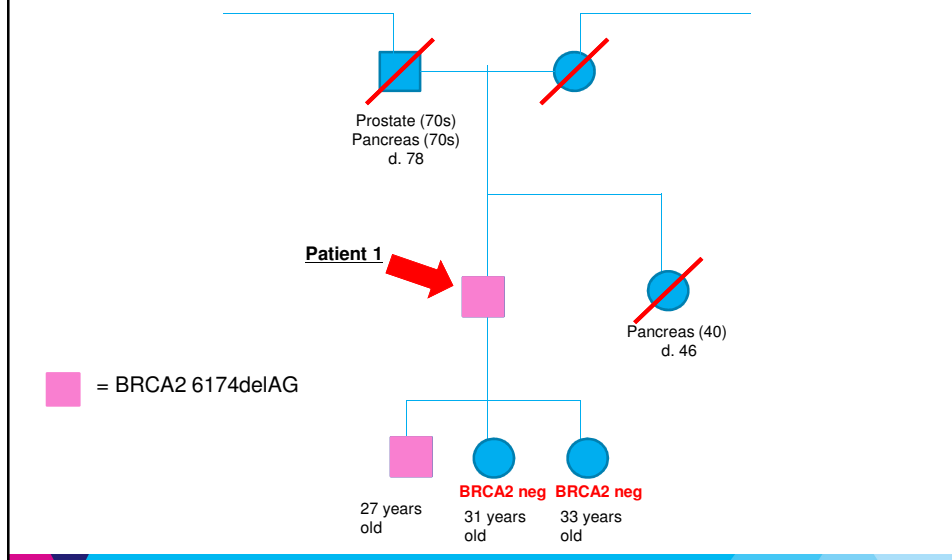
SURGICAL INTERVENTION

- Total pancreatectomy

PATHOLOGY RESULTS

- **Pancreatic adenocarcinoma** with adjacent **IPMN** and **multifocal PanIN2**

GENETIC TESTING

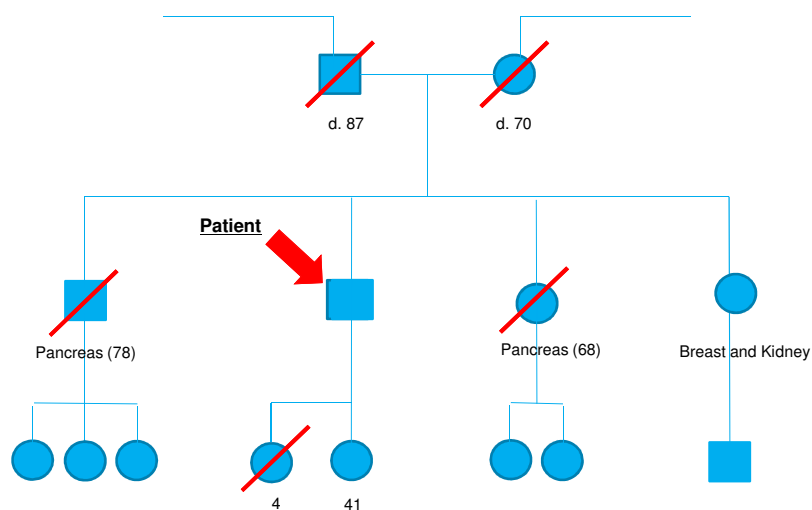


PATIENT CASE #2

PATIENT PRESENTATION - 2

- Sex: Male
 - Age: 73
 - Ashkenazi Jewish: Yes
 - Cigarette Use: 2nd hand smoke
 - Alcohol Use: Occasional
 - Diabetes Mellitus: Yes
 - Pancreatitis: No
 - Cancer History: None
 - Past Medical History: hypertension, cholesterol, ulcerative colitis
- **Physical Exam**
 - Normal
 - **Laboratory Exam**
 - Normal

FAMILY HISTORY

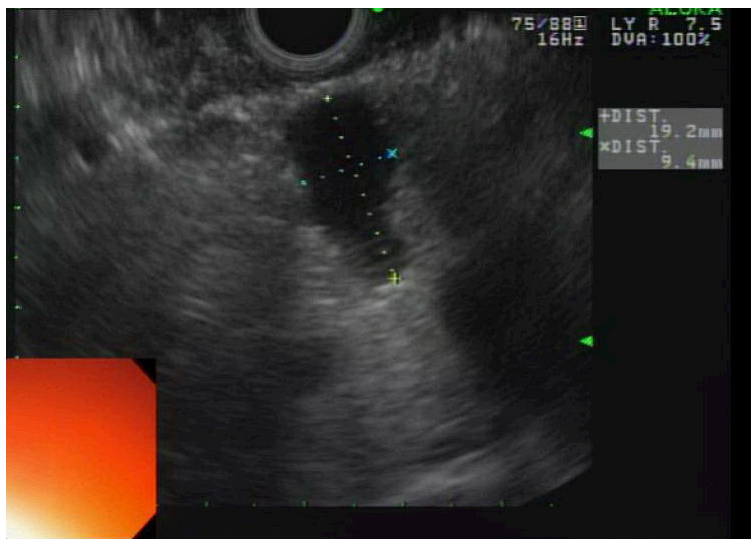


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RECOMMENDATIONS

- EUS
- MRI
- Genetic testing

Endoscopic Ultrasound



CEA was 121.47 NG/ML and cytology from the FNA revealed rare atypical glandular cells with dysplastic changes

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Magnetic Resonance Imaging



Cystic lesion in the pancreatic neck/body and is oblong shaped, measuring 3.4 x 1.3 x 1.1 cm

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SURGICAL INTERVENTION

- Distal pancreatectomy

PATHOLOGY RESULTS

- Two **intraductal papillary mucinous neoplasms** (IPMNs), predominantly involving branch ducts.
- The IPMN is lined by gastric foveolar type epithelium with up to **severe dysplasia**.
- No invasive carcinoma seen.

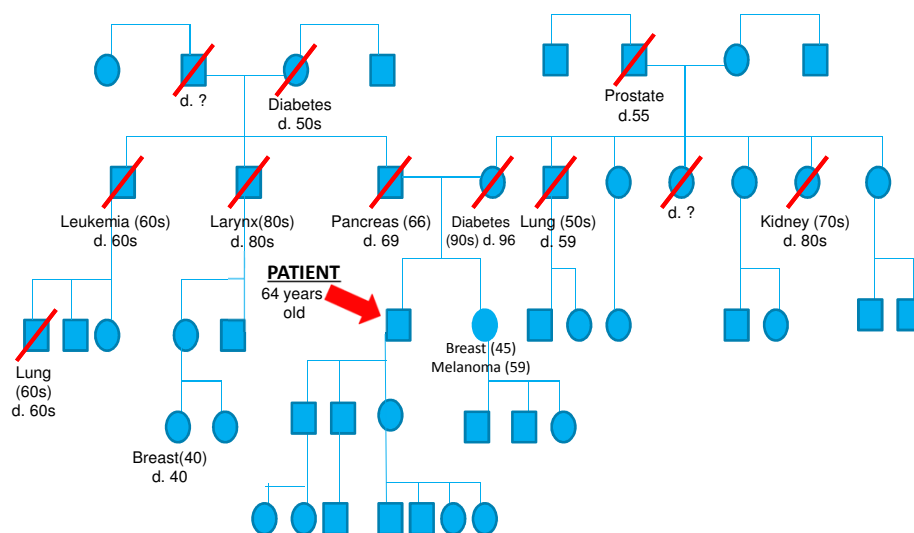
PATIENT CASE #3

Patient #3

INITIAL CONSULT

- Sex: Male
- Age: 65
- Ashkenazi Jewish: Yes
- Cigarette Use: Discontinued (smoked for 36 years; 1.5 ppd)
- Alcohol Use: 2-3 vodka/week
- Diabetes Mellitus: Yes (64 years old)
- Pancreatitis: No
- Cancer Hx: None
- Past Medical Hx:
 - GERD (35 years old)
 - Colon polyps (64 years old)
 - Barrett's Esophagus (64 years old)
- **Physical Exam**
Normal

FAMILY HISTORY

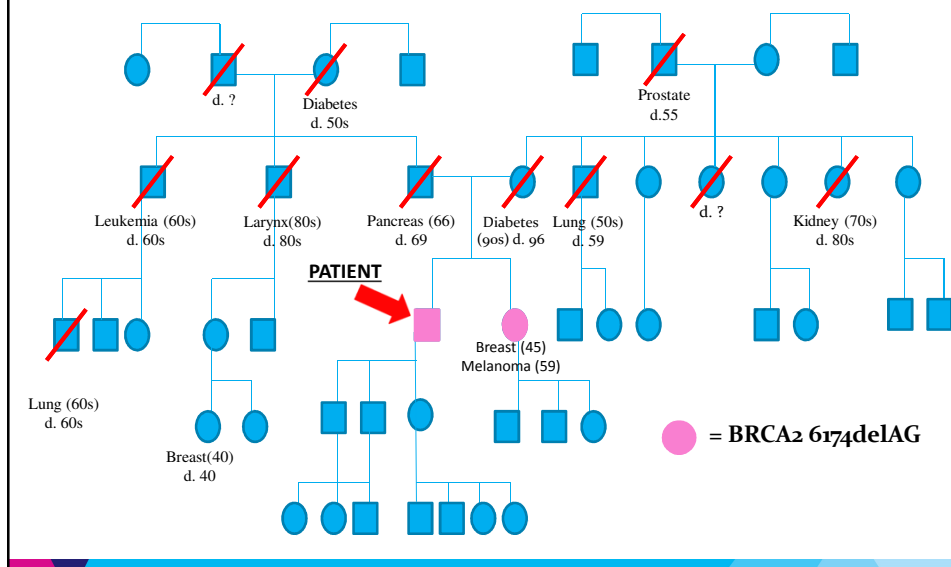


Patient #3

RECOMMENDATIONS

- Genetic testing
 - Test sister first

GENETIC TESTING

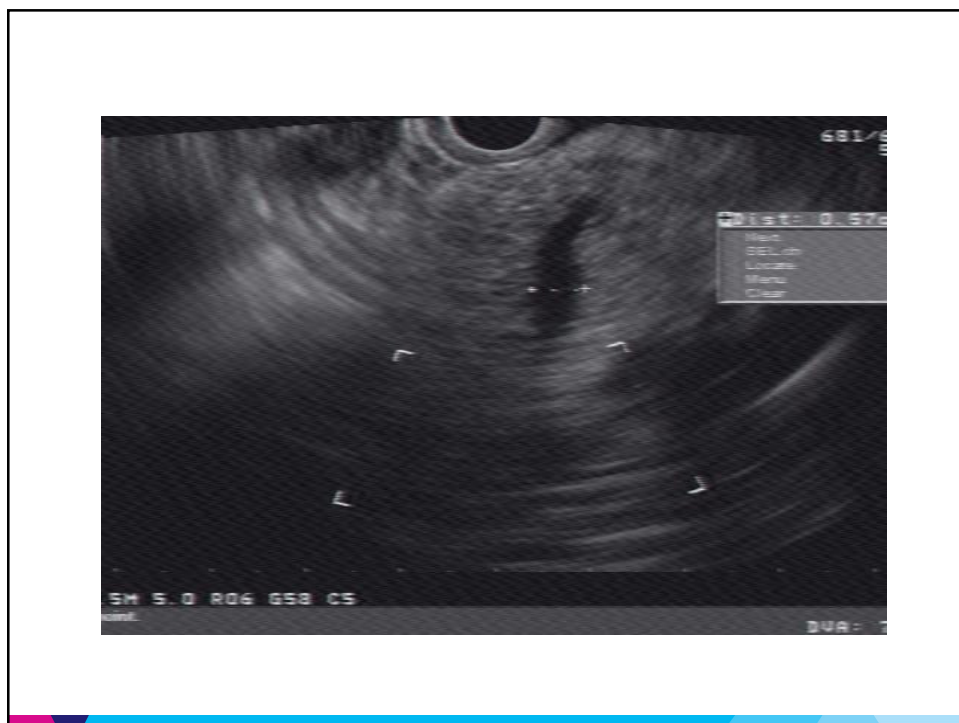
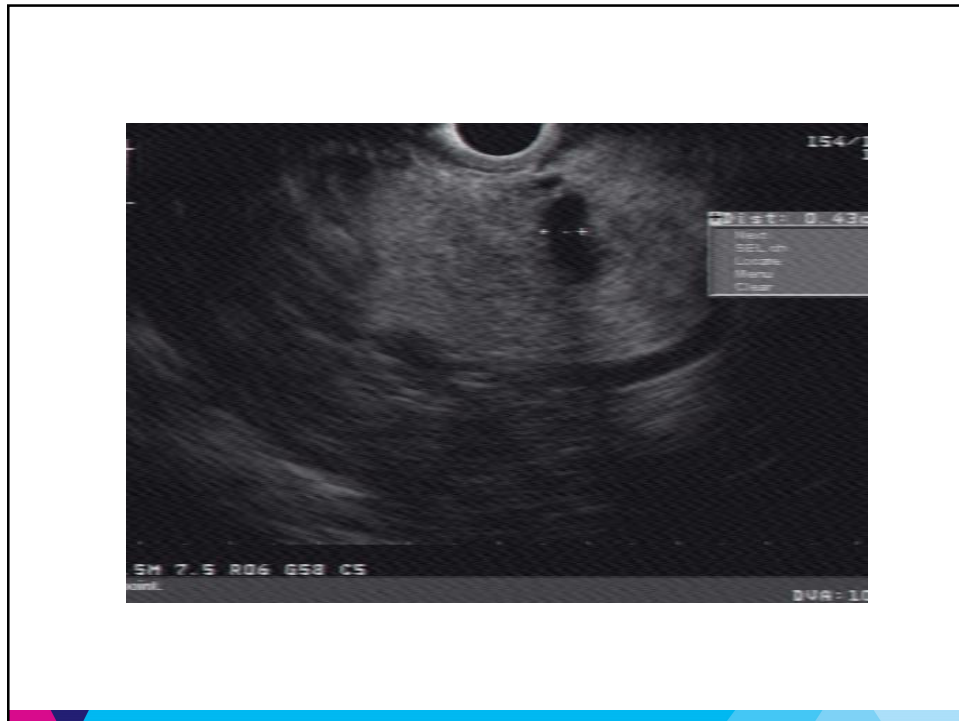


Patient #3

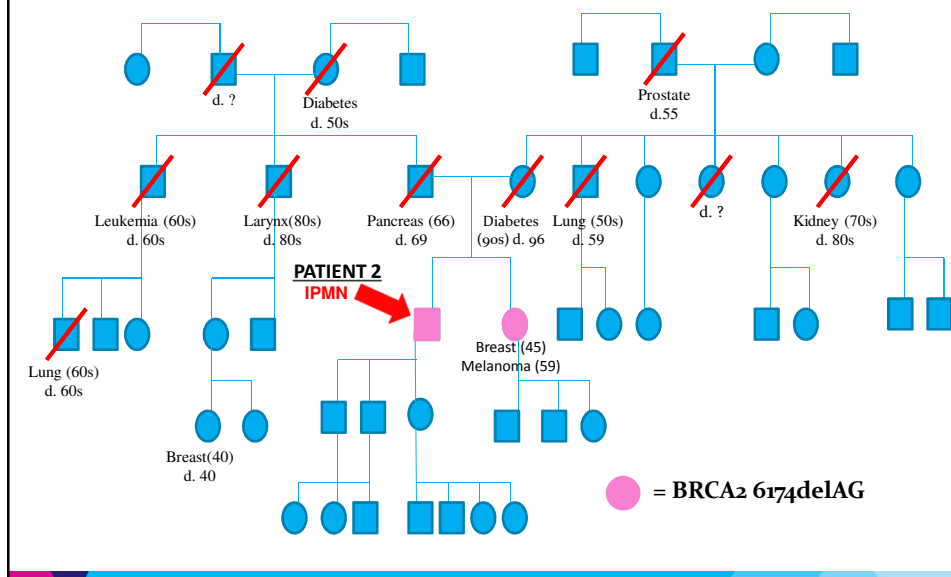
RECOMMENDATIONS

- **Laboratories (normal)**
- **EUS (secretin protocol)**
- **MRI (secretin protocol)**

MRI and EUS
=
Cystic changes
Irregular Ducts



GENETIC TESTING



Patient #3

SURGICAL INTERVENTION (Sister)

- Prophylactic hysterectomy and oophorectomy

Patient #3

PATHOLOGY RESULTS (Sister)

- Ovarian papillary serous adenocarcinoma

Summary

- Several genetic syndromes contribute to the risk of pancreatic cancer
- Smoking is the largest identifiable and modifiable risk factor
- Pre-cancerous lesions can be identified before the development of pancreatic cancer
- Genetic counseling and testing is an important part of pancreatic cancer screening, prevention and management
- More work is required to understand the genetics of pancreatic cancer

Thank You!



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