Screening in familial and hereditary Pancreatic Cancer

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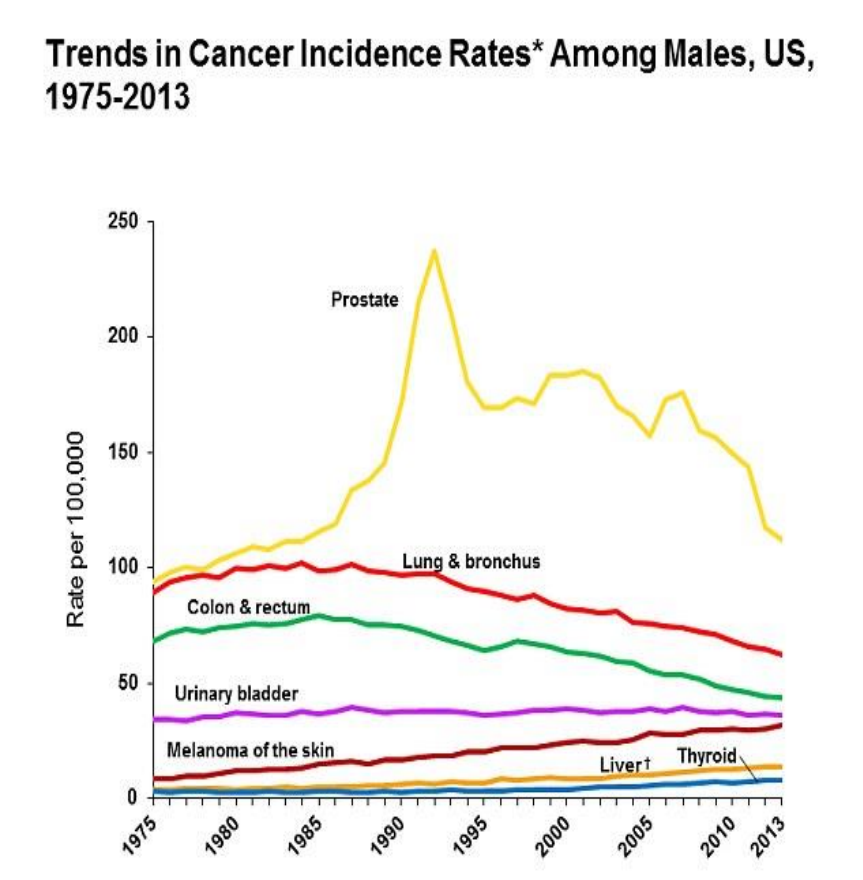
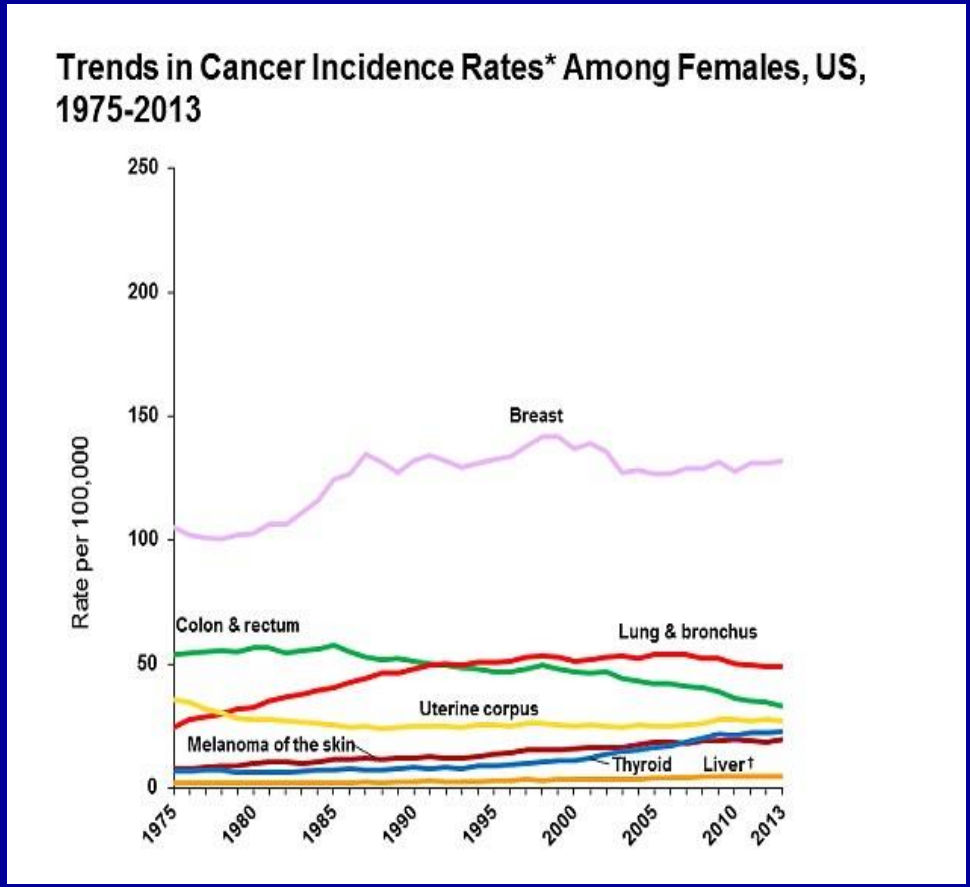
US Incidence

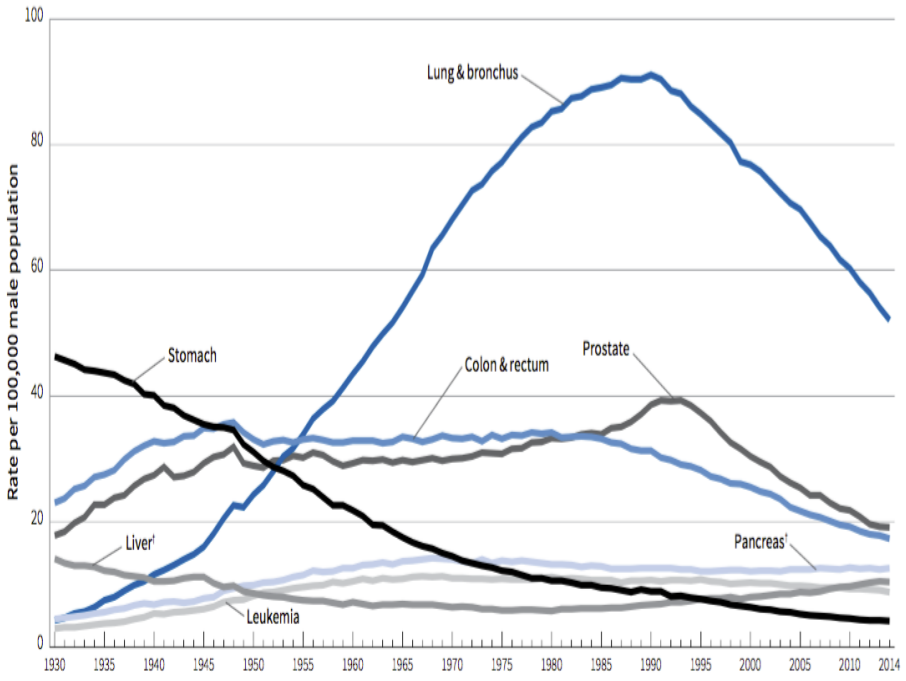




Siegel, R. L., Miller, K. D. and Jemal, A. (2017), Cancer statistics, 2017. CA: A Cancer Journal for Clinicians, 67: 7–30. doi:10.3322/caac.21387

US Mortality

Figure 1. Trends in Age-adjusted Cancer Death Rates* by Site, Males, US, 1930-2014

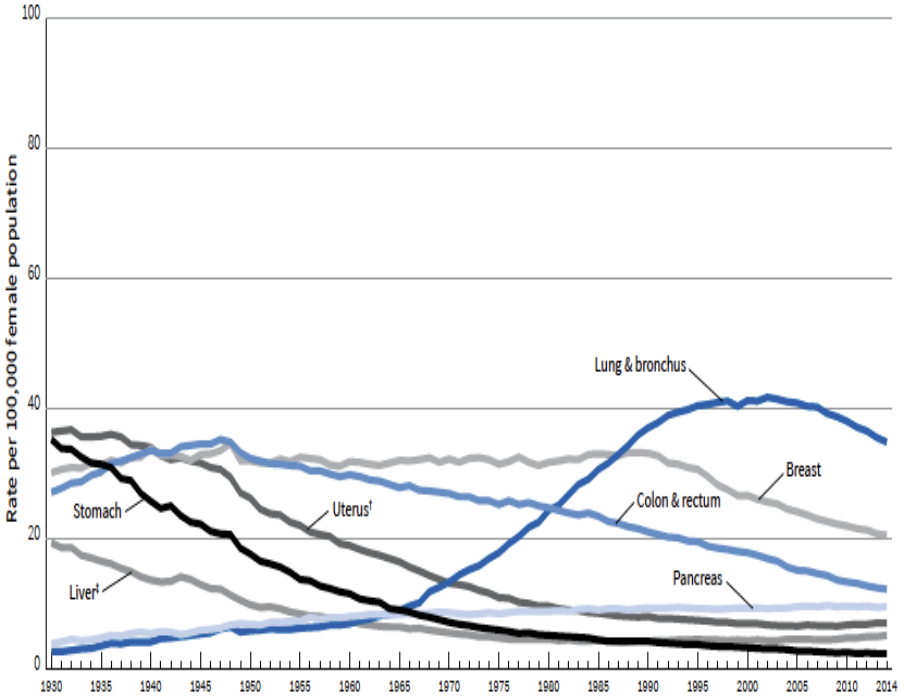


*Per 100,000, age adjusted to the 2000 US standard population. †Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, uterus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959 and US Mortality Data 1960 to 2014, National Center for Health Statistics, Centers for Disease Control and Prevention.

Figure 2. Trends in Age-adjusted Cancer Death Rates* by Site, Females, US, 1930-2014



*Per 100,000, age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined. ‡The mortality rate for liver cancer is increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, uterus, and colon and rectum are affected by these coding changes.

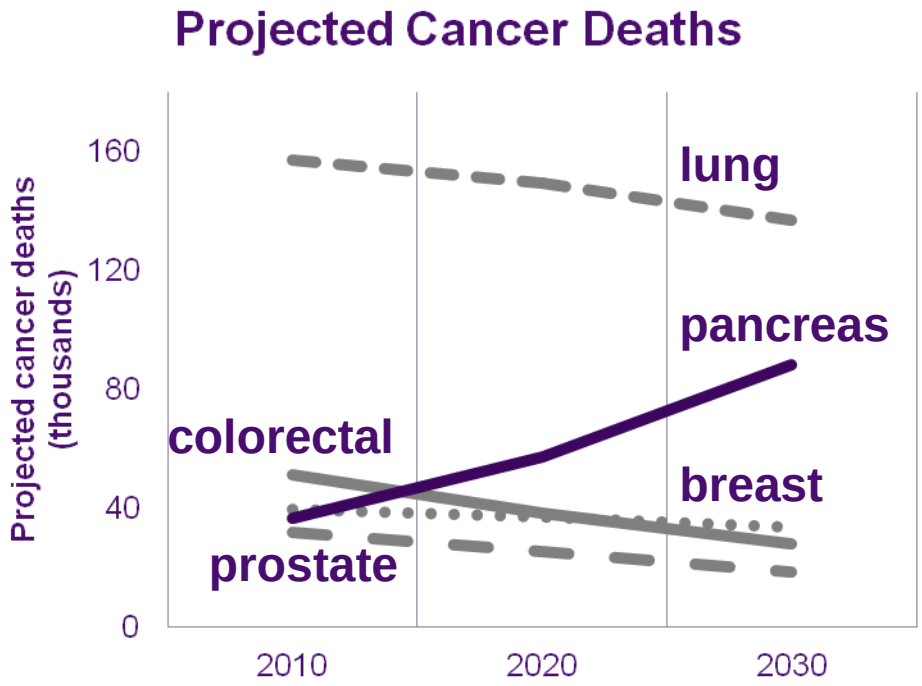
Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2014, National Center for Health Statistics, Centers for Disease Control and Prevention.

American Cancer Society. *Cancer Facts & Figures 2017.* Atlanta: American Cancer Society; 2017

Moving from 4th to 2nd place

- Pancreatic cancer is the only one of the top 5 cancer killers for which deaths are projected to INCREASE.

- As early as 2015, pancreatic cancer is projected to surpass breast and colorectal cancer and become the 2nd leading cause of cancer death



Age-Specific SEER Incidence Rates, 2007-2011

Age at Diagnosis	All Races	
	Both Sexes	Males
20-24	0.1	-
25-29	0.2	0.2
30-34	0.5	0.4
35-39	1.0	1.1
40-44	2.7	3.0
45-49	5.6	6.3
50-54	10.7	13.1
55-59	18.9	22.8
60-64	30.1	36.4
65-69	44.4	52.4
70-74	60.5	68.2
75-79	78.3	85.8
80-84	92.9	102.8
85+	101.2	109.5

SEER 18 areas. Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups)

http://seer.cancer.gov/csr/1975_2011/browse_csr.php?sectionSEL=22&pageSEL=sect_22_table.07.html

Pancreatic cancer risk factors: results from published meta-analyses

Exposure/Condition	OR/RR	95% CI
Current cigarette smoking	2.2	1.7 - 2.8
Heavy alcohol (>9 drinks/day)	1.6	1.2-2.2
Diabetes 10+ years	1.36	1.19-1.55
Body Mass Index (5 unit increments)	1.1	1.07-1.14
Waist-to-Hip ratio (0.1 unit increments)	1.19	1.09-1.31
History of allergies	0.73	0.64-0.84
Chronic Pancreatitis	5.8	2.1-15.9

Courtesy of Paige Bracci

Table 4 – Summary relative risks for the association between diabetes and pancreatic cancer according to diabetes duration.

Diabetes duration, years	No. of studies	Relative risk 95%	Confidence interval
<1	3	5.38	3.49–8.30
1–4	5	1.95	1.65–2.31
5–9	4	1.49	1.05–2.12
>10	4	1.47	0.94–2.31
>1	14	1.96	1.60–2.40
>5	11	1.83	1.38–2.43

Qiwen Ben, European Journal of Cancer 47 (2011) 1928–1937

Identifying Hereditary Risk

Why is this important?

1. Screening unaffected family members

2. Treatment selection

Definition of Hereditary Pancreatic Cancer

- Recognized genetic syndromes with a known germline mutation associated with an increased risk of PC
- Two or more cases of PC (with at least a pair of FDR) without a known mutation.
  - This has been called "familial pancreatic cancer"

Courtesy of Randall Brand

Risk for Developing Pancreatic Cancer in "Familial Pancreatic Cancer" by Family History, Age and Smoking History

Overall	6.79 (4.54 to 9.75)*
Three or more FDR	17.02 (7.34 to 33.5)*
Two FDR	3.97 (1.59 to 8.2)*
One FDR	6.86 (3.75 to 11.04)*
Young-onset kindred	9.31 (3.42 to 20.28)*
Late-onset kindred	6.34 (4.02 to 9.51)*
Smokers	9.09 (4.97 to 15.25)*
Nonsmokers	6.38 (3.02 to 11.15)*

* $p < 0.005$

Brune, et al. JNCI 2010

Syndromes Associated with Pancreatic Adenocarcinoma

Syndrome	**Relative Risk of PC**	**Gene**
Familial Atypical Multiple Mole Melanoma (FAMMM)	13-22 fold	p16
Familial Breast and Ovarian	< 5 fold	BRCA1 or 2
Fanconi Anemia, Breast CA	Unknown	PALB2
FAP	5 fold	APC
Hereditary Non-polyposis Colon Cancer (HNPCC)	1.5-9 fold	MLH1, MSH6 MSH2, PMS2
Peutz-Jeghers Syndrome	Up to 100 fold	STK11/LKB1
Hereditary Pancreatitis	53 fold	PRSS1
Cystic Fibrosis	2.6 to 32 fold	CFTR
Ataxia -telangiectasia	Unknown	ATM

Courtesy of Randall Brand

Definition of Cancer Screening

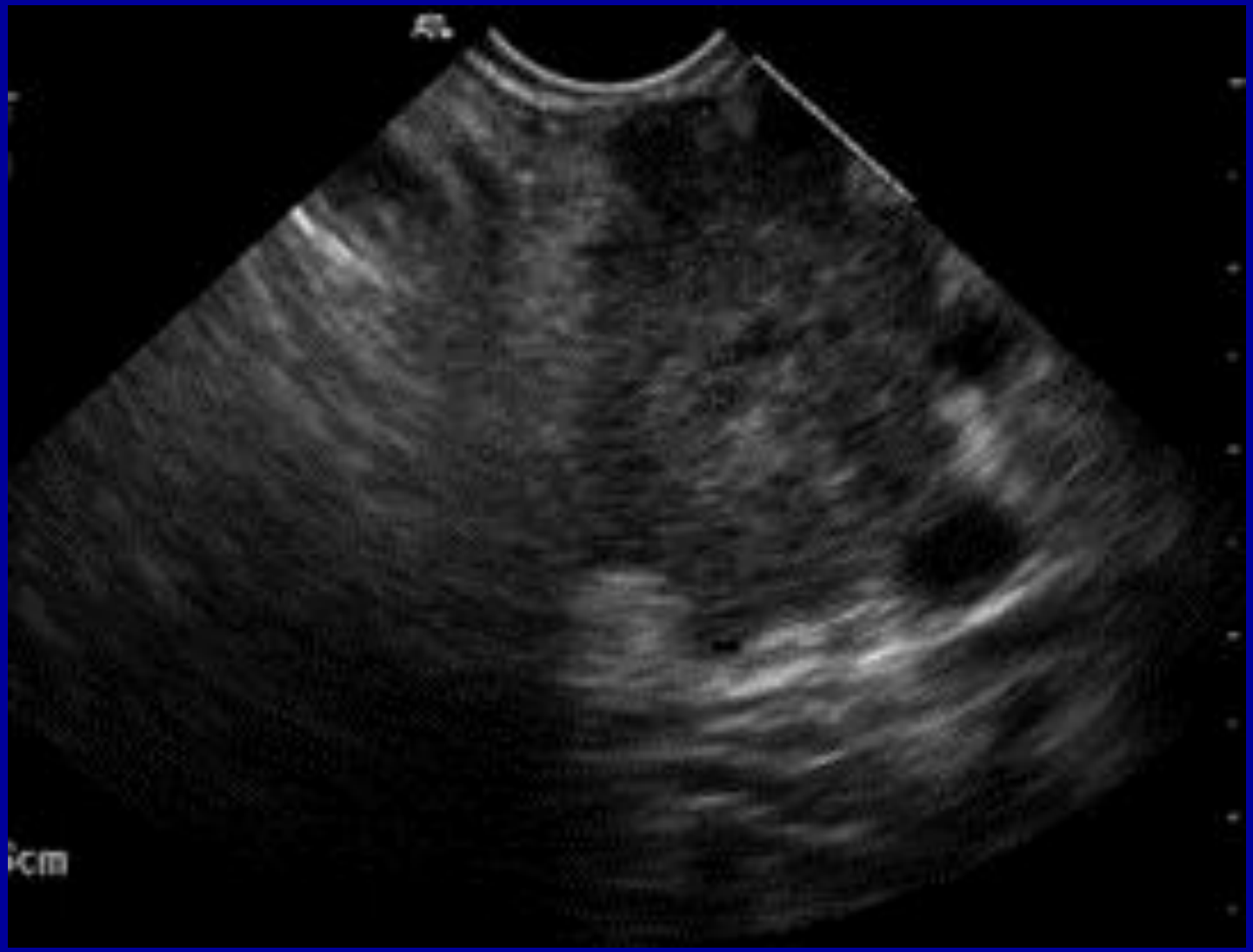
- Surveillance: Testing in asymptomatic high-risk individuals
- Screening: Testing in setting of asymptomatic general population
- Diagnostic: Testing in setting of symptoms

Courtesy of Randall Brand

Imaging of the Pancreas

- Endoscopic ultrasound (EUS)
- Computed tomography (CT)
- Endoscopic Retrograde Cholangiopancreatography (ERCP)
- Magnetic resonance Cholangiopancreatography (MRCP)

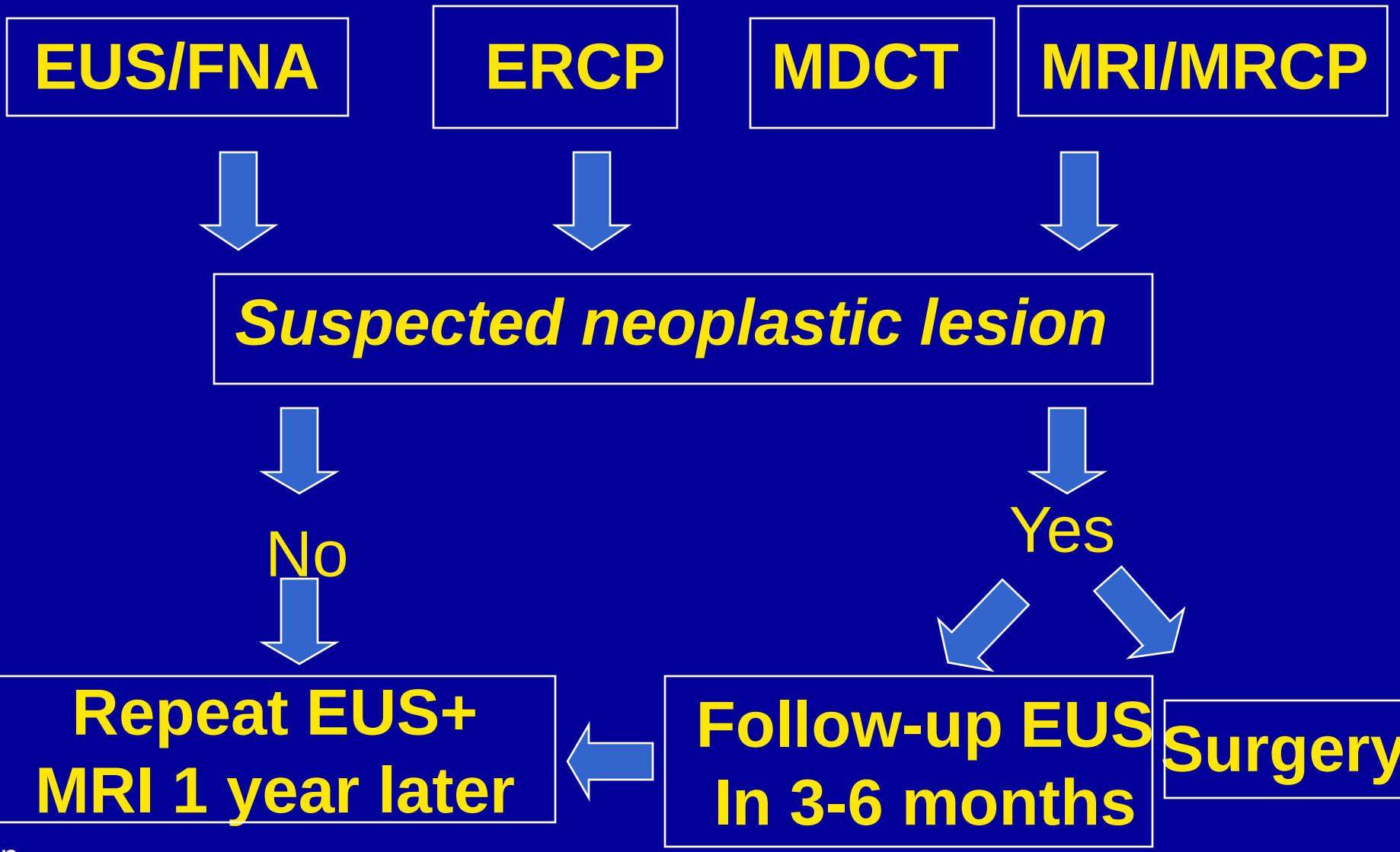
Endoscopic ultrasound (EUS)



Poley, Am J Gastro 2009
Canto et al, Clin Gastro Hepatol 2006

Courtesy of Benjamin Yeh

Johns Hopkins Approach

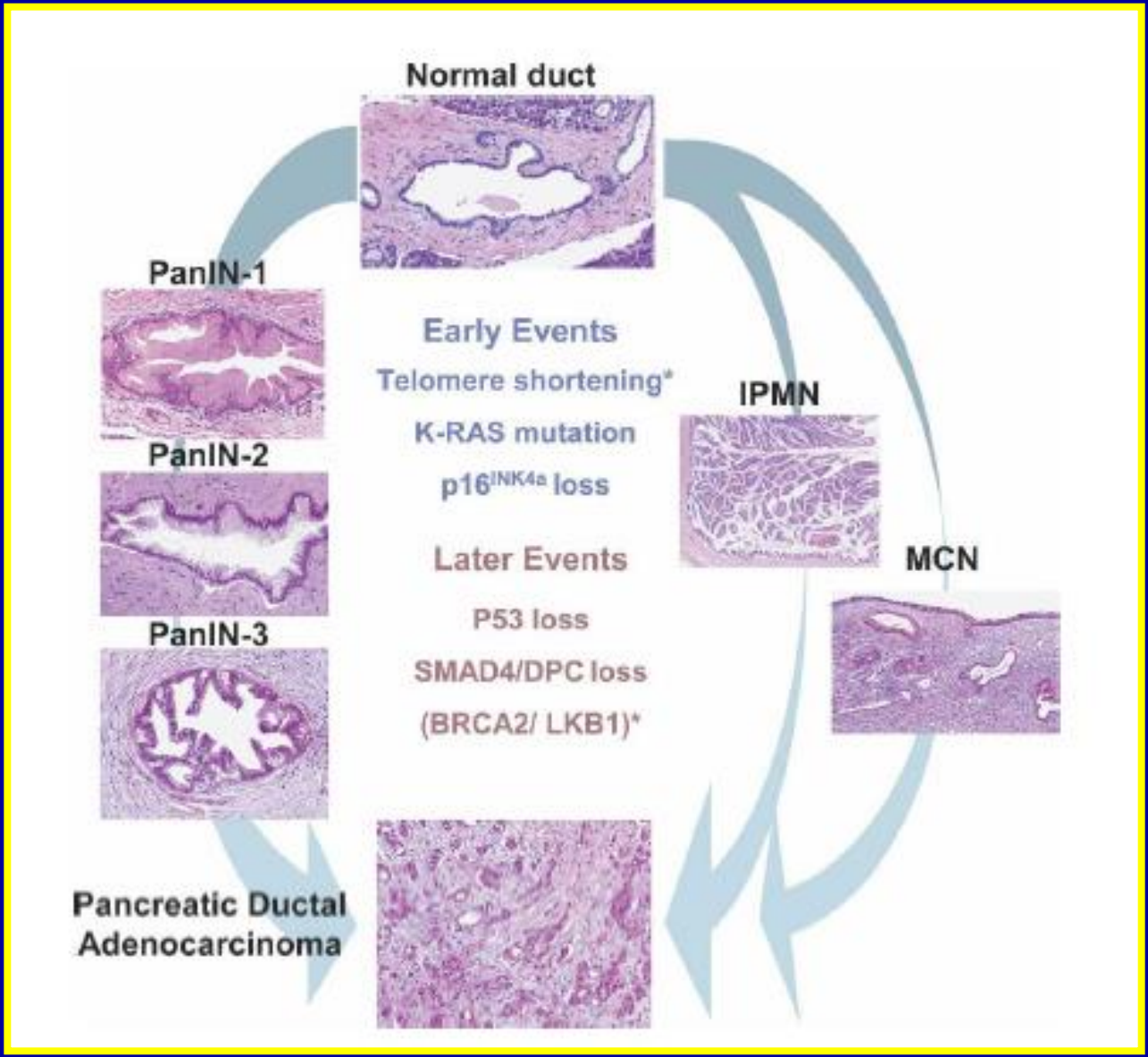


Familial PC Screening Programs

	Popn	Tests	Dx Yield
Canto 2004	FPC , PJS	EUS	2/38 (5.3%)
Canto 2006	FPC , PJS	EUS + CT	8/78 (10.2%)
Poley 2009	FPC, PJS, p16, BRCA	EUS	10/44 (23%)
Langer 2009	FPC ,BRCA	EUS + MRCP	3/76 (3.9%)
Verna 2010	FPC, BRCA2, p16	EUS or MRCP	6/52 (12%)
Ludwig 2011	FPC, BRCA	MRCP, EUS	9/109 (8.3%)
Al-Sukhni 2011	FPC, BRCA, p16, PJS	MRI only	84/262 (32%)
Schneider 2011	FPC, BRCA, PALB2	EUS+MRCP	4/72(5.5%) – 9/72(12.5%)
Vasen 2011	p16	MRI only	16/79(20%)
Canto 2012	FPC,BRCA, PJS	EUS,MRI,CT	5/216(2.3%)- ((92/216(42%)

Courtesy of Marcia Canto

Genetic abnormalities associated with the initiation and progression of pancreatic ductal adenocarcinoma



Hezel et al, Genes Dev. 2006 20: 1218-1249

Treatment Selection

- MSI high tumors– mutation involving mismatch repair
- Mutations involving DNA damage repair

Phase 2 Study of MK-3475 in Patients With Microsatellite Unstable (MSI) Tumors

- Oral presentation by Dung Le ASCO 2016

Study Design

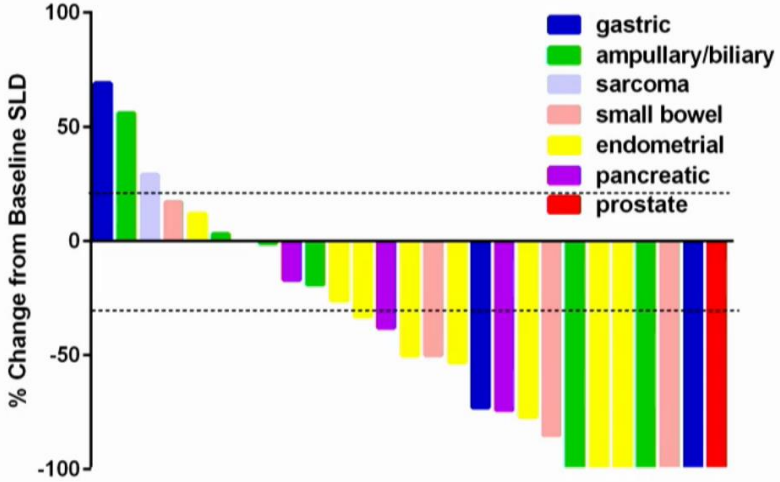
Colorectal Cancers		Non-Colorectal Cancers
Cohort A Deficient in Mismatch Repair (n=25)	Cohort B Proficient in Mismatch Repair (n=25)	Cohort C Deficient in Mismatch Repair (n=21)

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Mismatch repair testing was performed locally using standard IHC for MMR deficiency or PCR-based test for microsatellite instability

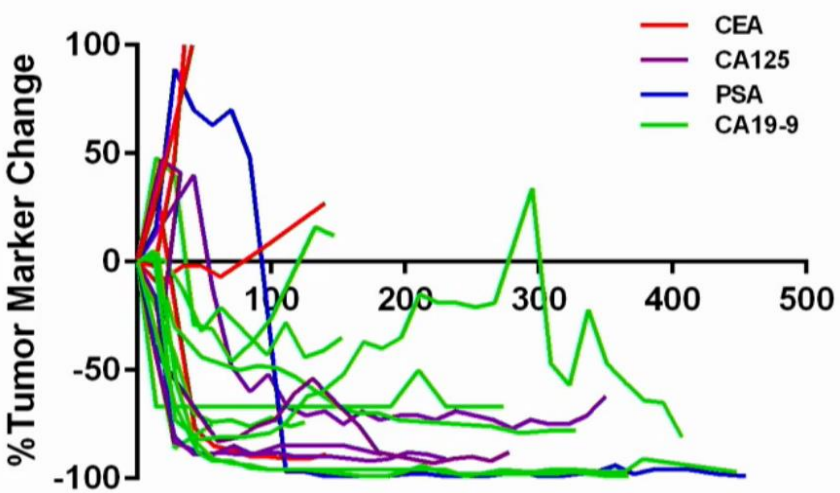
Ongoing Expansion (n=+50)

Repair of insertion/deletion loops

Target Lesion Measurements



Tumor Marker Kinetics



Objective Responses

Type of Response-no (%)	MMR-deficient non CRC n=30
Complete Response	9 (30)
Partial Response	7 (23)
Stable Disease (Week 12)	5 (17)
Progressive Disease	7 (23)
Not Evaluable[1]	2 (7)
Objective Response Rate (%)	16 (53)
95% CI	36-70
Disease Control Rate (%)	21 (70)
95% CI	52 - 83
Median Follow Up	10 mos

[1]Patients were considered not evaluable if they did not undergo a 12 week scan

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Case Study

- 47 year old man with Lynch Syndrome diagnosed and a prior history of CRC
- Presented with locally advanced PDAC- May 2015
- Responds well to FOLFIRINOX but progresses in April 2016
- Begins treatment with pembro in May 2016 and responds
- Response continues today

CA 19-9

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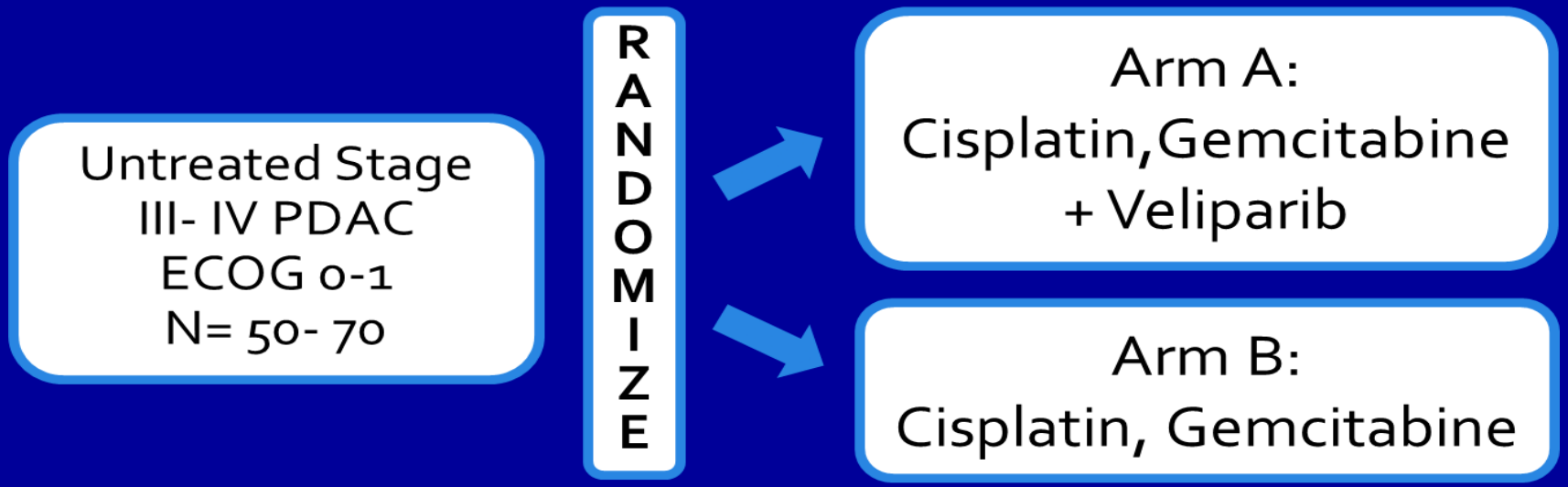
Randomized Phase II
Cisplatin, Gemcitabine +/- Veliparib
Germline BRCA/PALB2

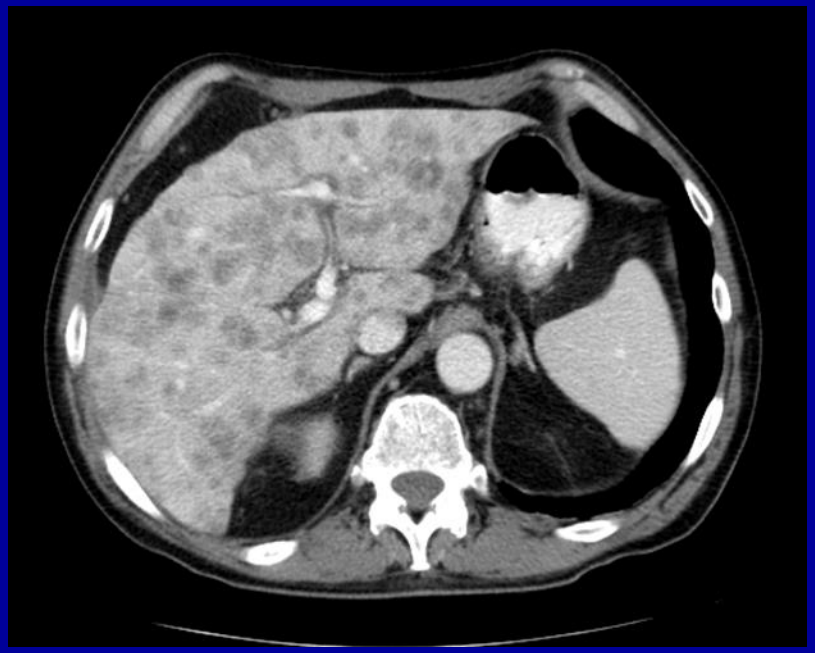


Randomization 1: 1
Primary Endpoint: Response Rate

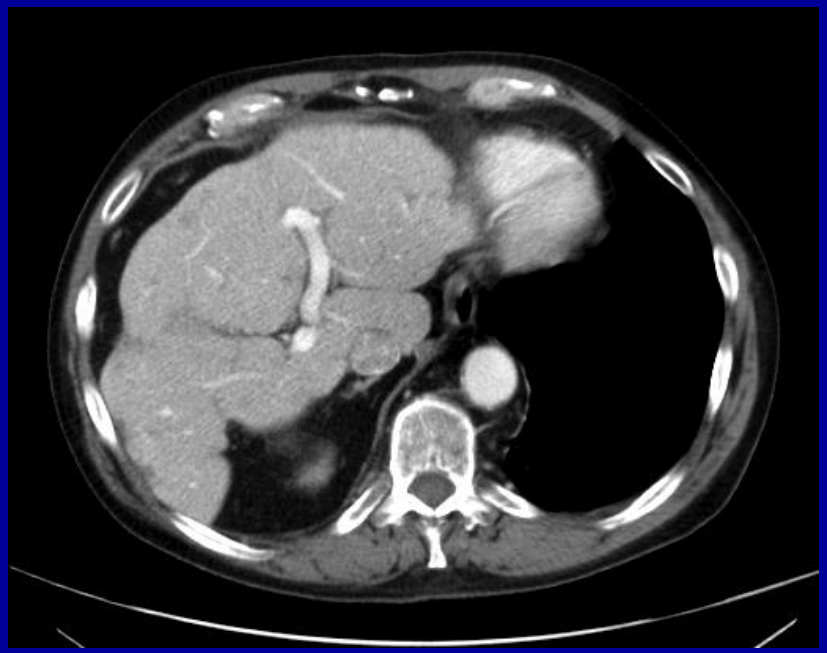
NCT01585805 O'Reilly, EM, Lowery, MA, Kelsen, DP

Experimental Arm A
Cisplatin-Gem-Veliparib: gBRCA2

12/12/201x
Ca 19-9 9,858
CEA 19.8



08/02/201x
Ca 19-9 152
CEA 2.7



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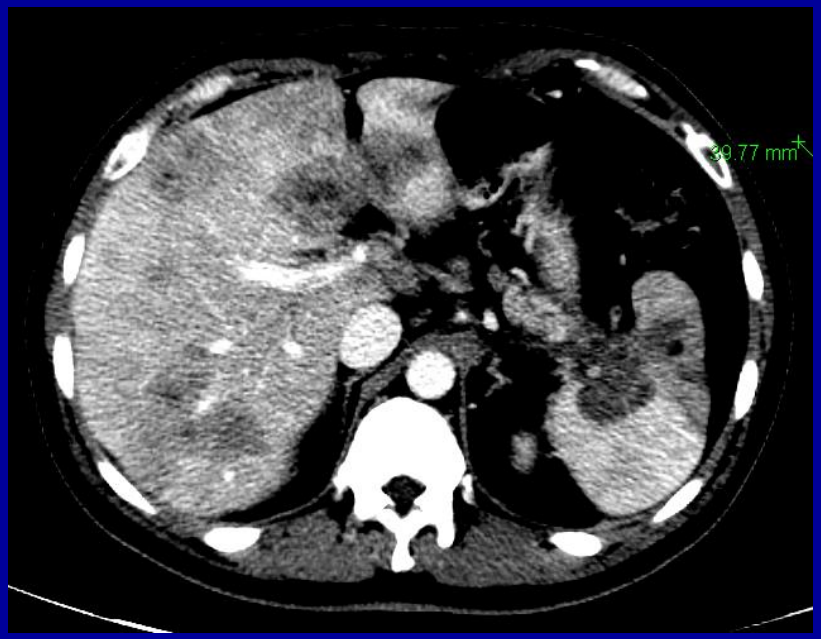
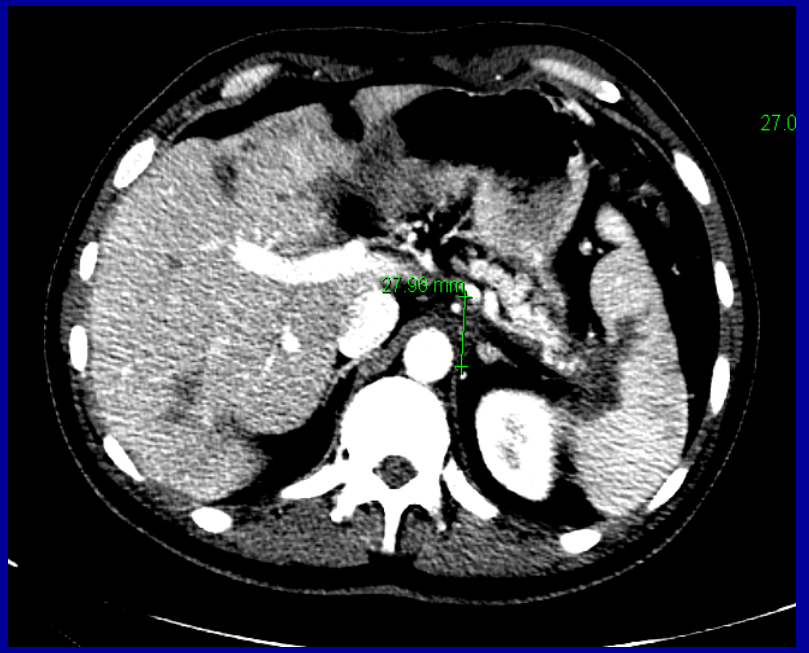
Courtesy of Eileen O'Reilly

Control Arm B
Cisplatin-Gem: gBRCA2

03/17/201x
Ca 19-9 170,495
CEA 136



07/30/201x
Ca 19-9 172
CEA 2.5



Take Home Lessons

- Take a good FH
- Do genetic counseling and mutation testing in patients with a FH of cancer or who are < 60 years old
- Recommend screening for family members in selected mutation carriers or in hereditary PDAC
- For MSI tumors, consider early use of a check point inhibitor
- For DDR mutations, consider gemcitabine and cisplatin, even in the adjuvant setting

Thank you!