

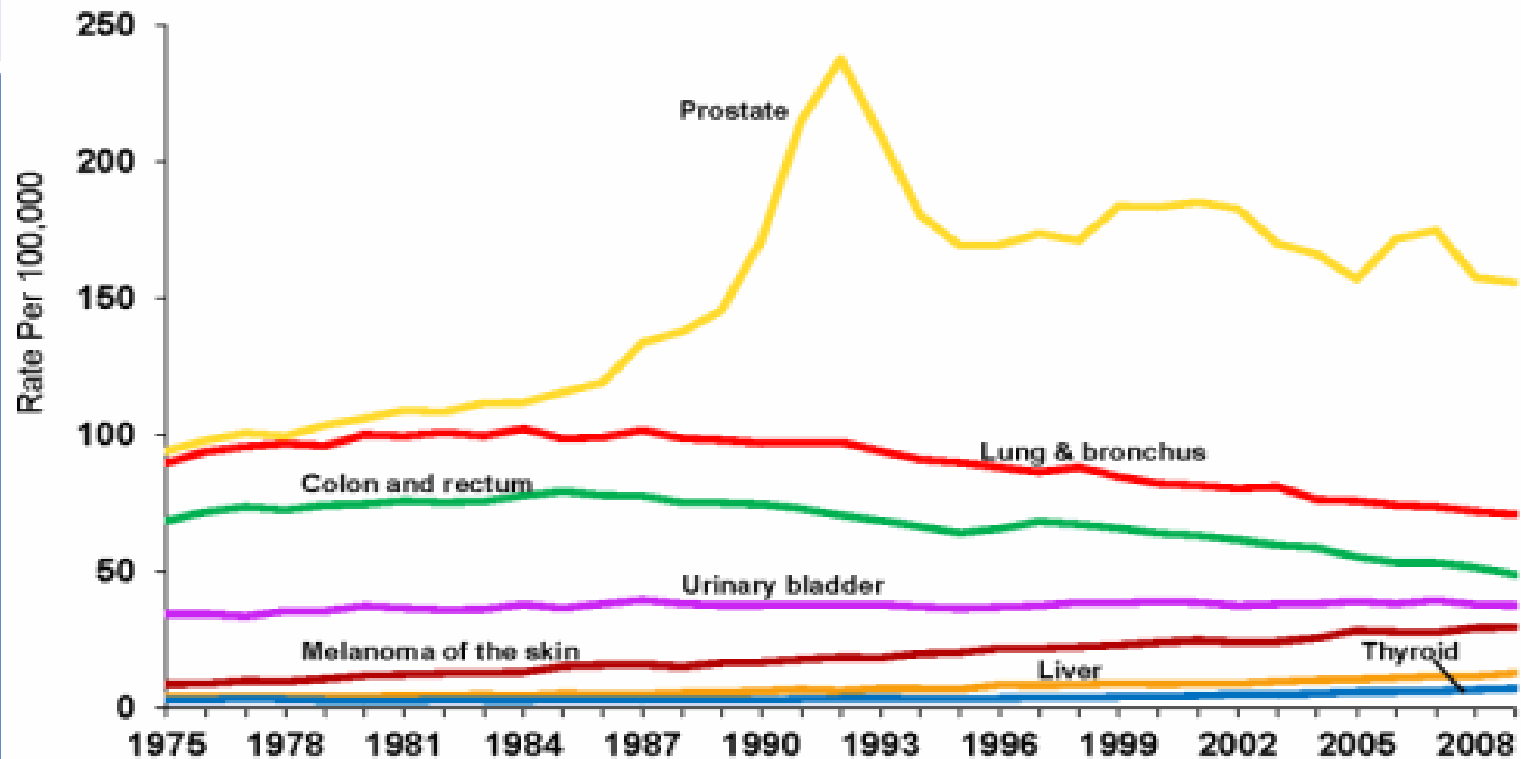
A photograph of the Golden Gate Bridge in San Francisco, California. The bridge is a large suspension bridge with two main towers and numerous suspension cables. It is surrounded by green trees and a blue sky with some clouds. The bridge is the central focus of the image.

Understanding Risk for Pancreatic Cancer

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US Incidence

Cancer Incidence Rates* Among Men, US, 1975-2009

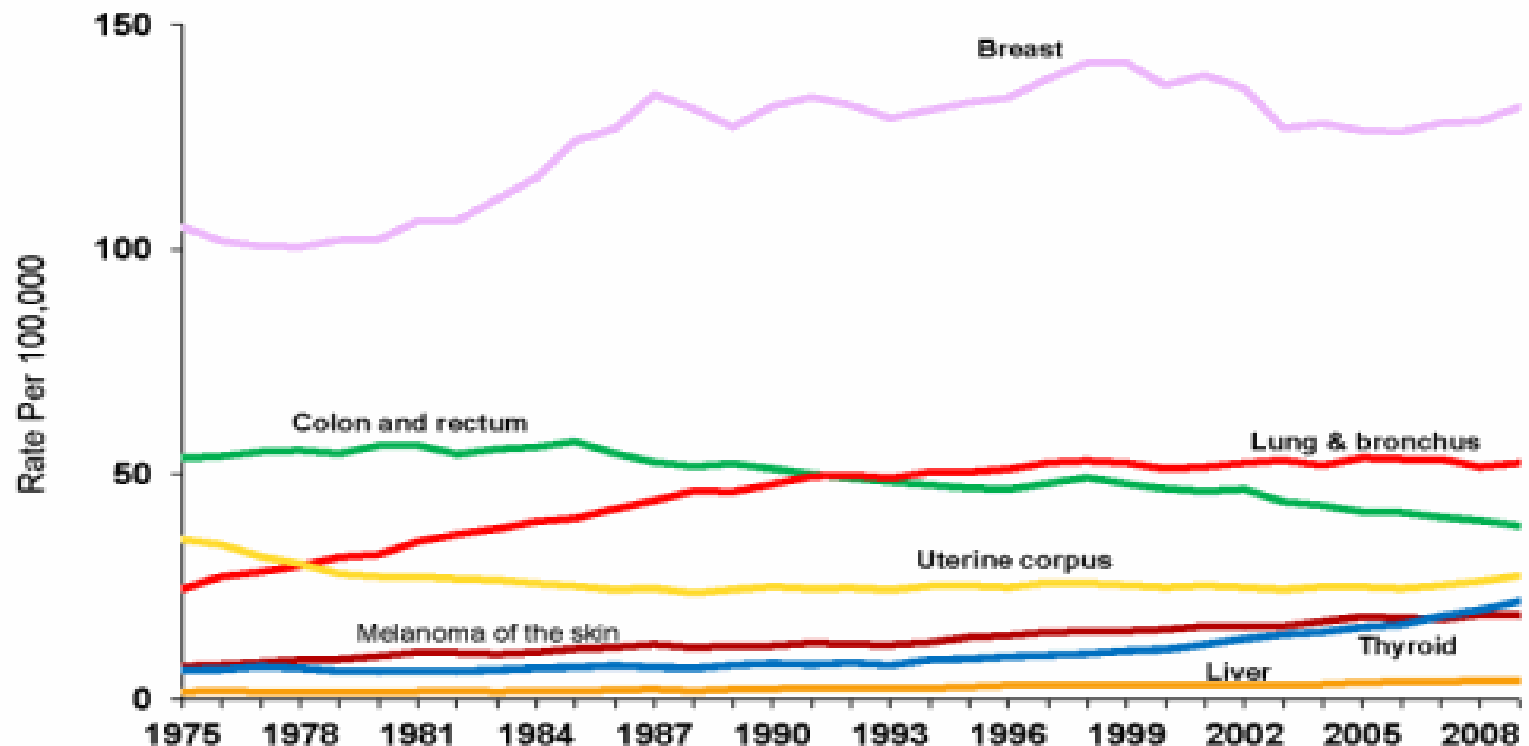


*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.

Source: Surveillance, Epidemiology, and End Results Program, Delay-adjusted Incidence database: SEER Incidence Delay-adjusted Rates, 9 Registries, 1975-2008, National Cancer Institute, 2012.

US Incidence

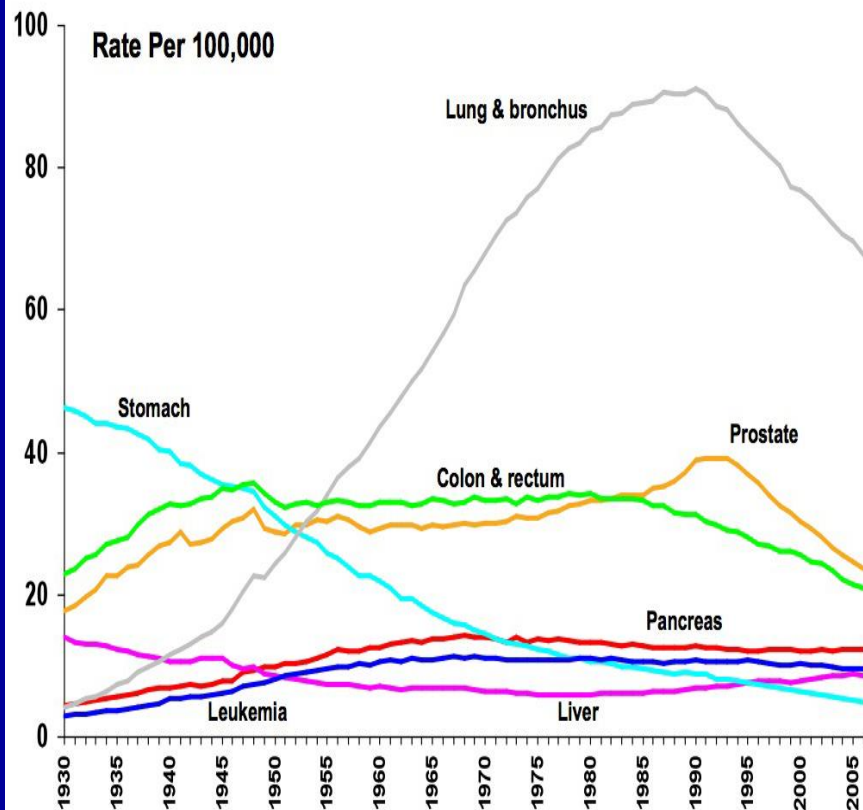
Cancer Incidence Rates* Among Women, US, 1975-2009



*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results Program, Delay-adjusted Incidence database:
SEER Incidence Delay-adjusted Rates, 9 Registries, 1975-2009, National Cancer Institute, 2012.

US Mortality

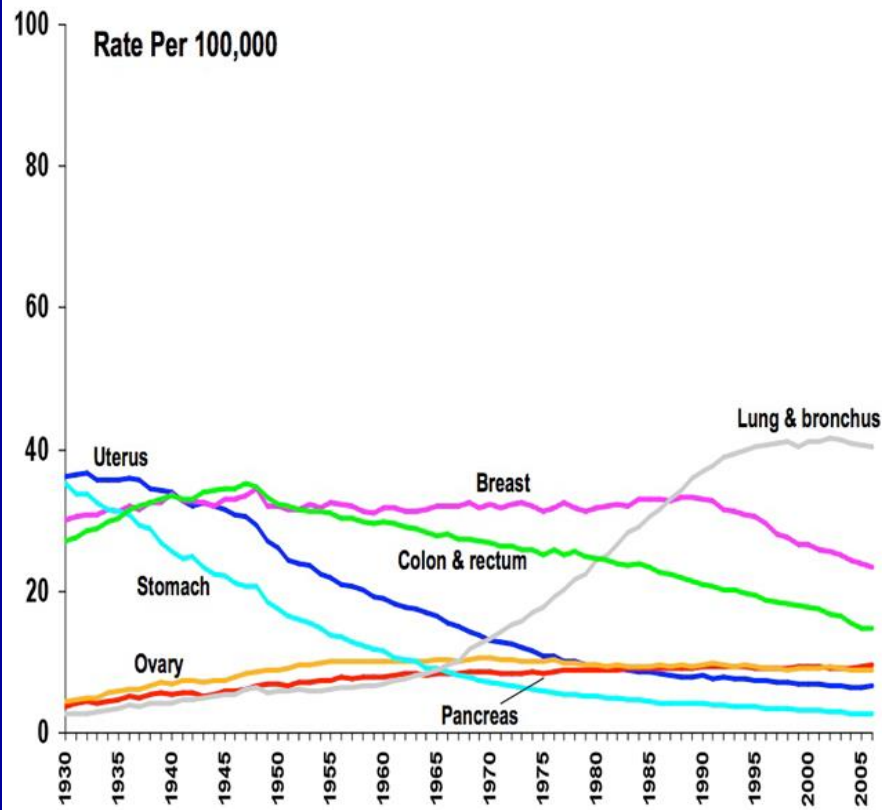
Cancer Death Rates* Among Men, US, 1930-2006



*Age-adjusted to the 2000 US standard population.

Source: US Mortality Data 1960-2006, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.

Cancer Death Rates* Among Women, US, 1930-2006



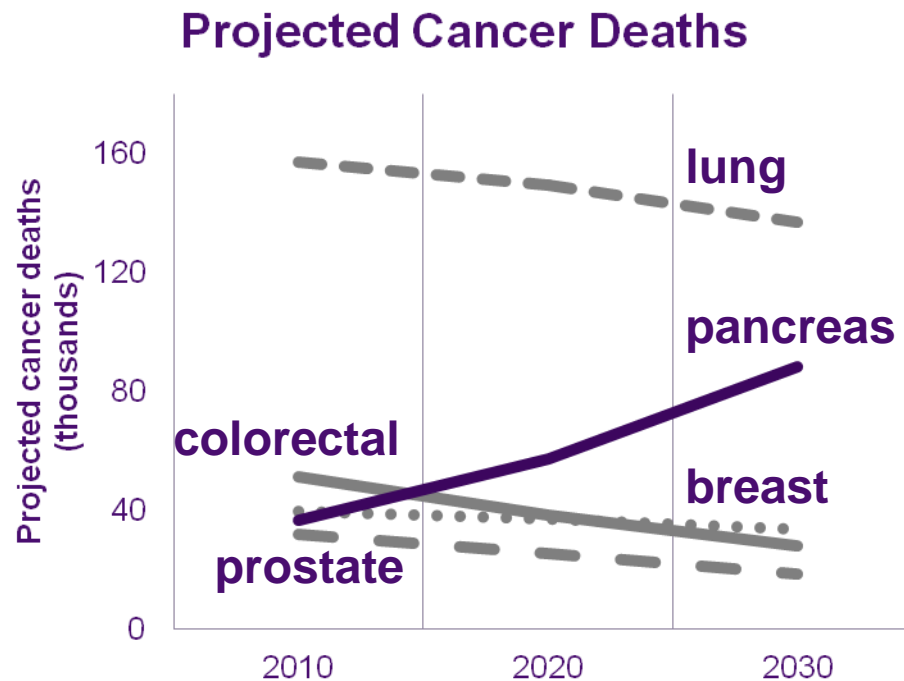
*Age-adjusted to the 2000 US standard population.

Source: US Mortality Data 1960-2006, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.

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



Progress in pancreatic
ductal adenocarcinoma
has been very slow!

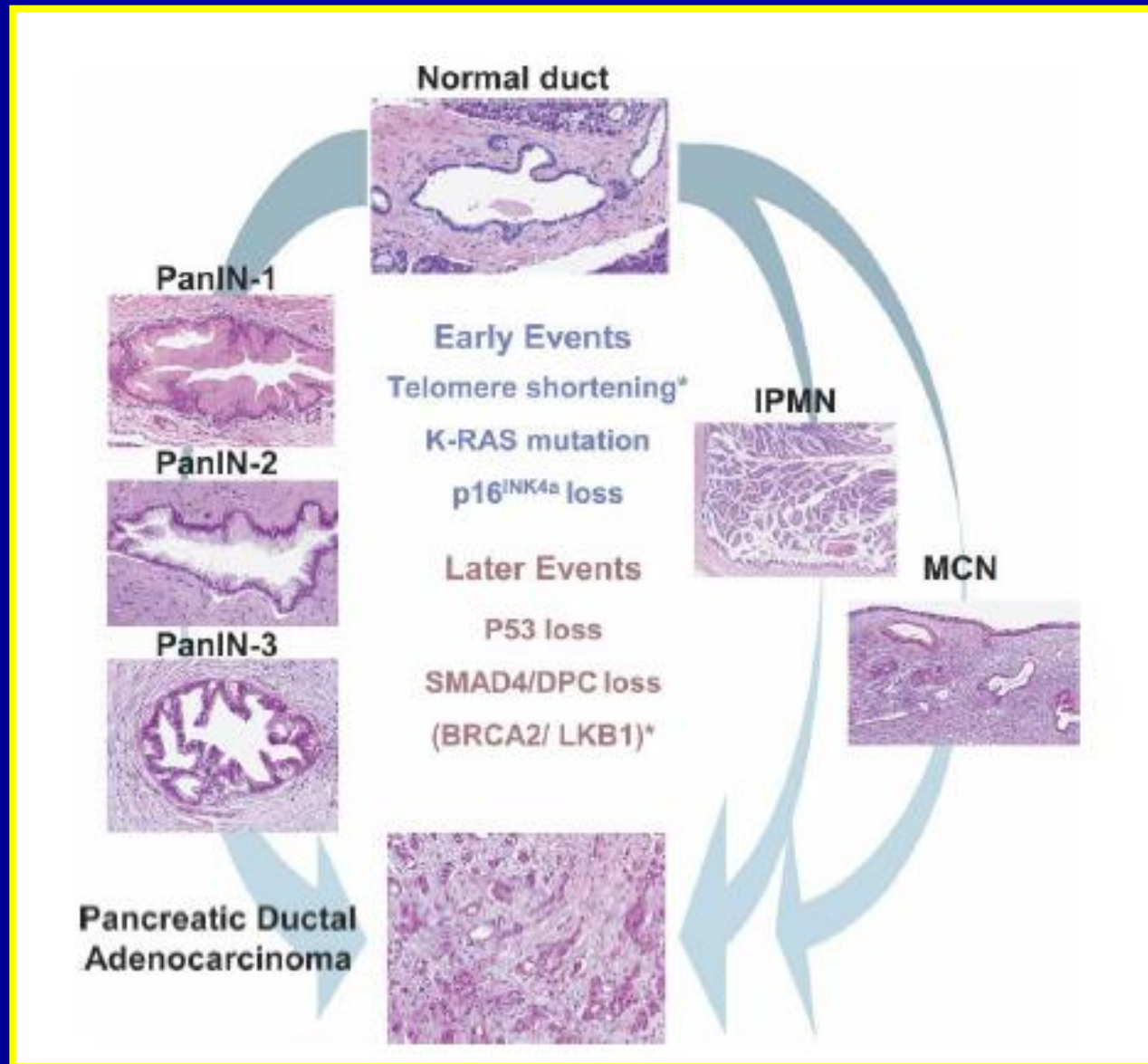
This is a very tough disease!

- 80% of patients are diagnosed with advanced unresectable disease
- 80% of patients who have resection relapse
- “Cure” rate is only 5-6%
- Median survival of patients with metastases without treatment is only about 3 months

Why is this disease so aggressive?

- No early symptoms
- Very early invasion and metastases
- Chemo-resistant (sanctuary?)
- Debilitating cytokine mediated symptoms

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



Age-Specific SEER Incidence Rates, 2007-2011

Age at Diagnosis	All Races			Whites			Blacks		
	Both Sexes	Males	Females	Both Sexes	Males	Females	Both Sexes	Males	Females
All ages	12.3	14.0	10.9	12.2	14.0	10.7	15.6	17.2	14.2
Under 65	4.0	4.8	3.3	4.0	4.7	3.3	5.7	7.0	4.7
65 and over	69.5	77.6	63.3	69.2	78.2	62.3	83.4	88.1	80.2
All ages (IARC world std)	7.4	8.6	6.4	7.3	8.5	6.3	9.7	11.0	8.

SEER 18 areas. Rates are per 100,000 and are age-adjusted to the IARC World Standard

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

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

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

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

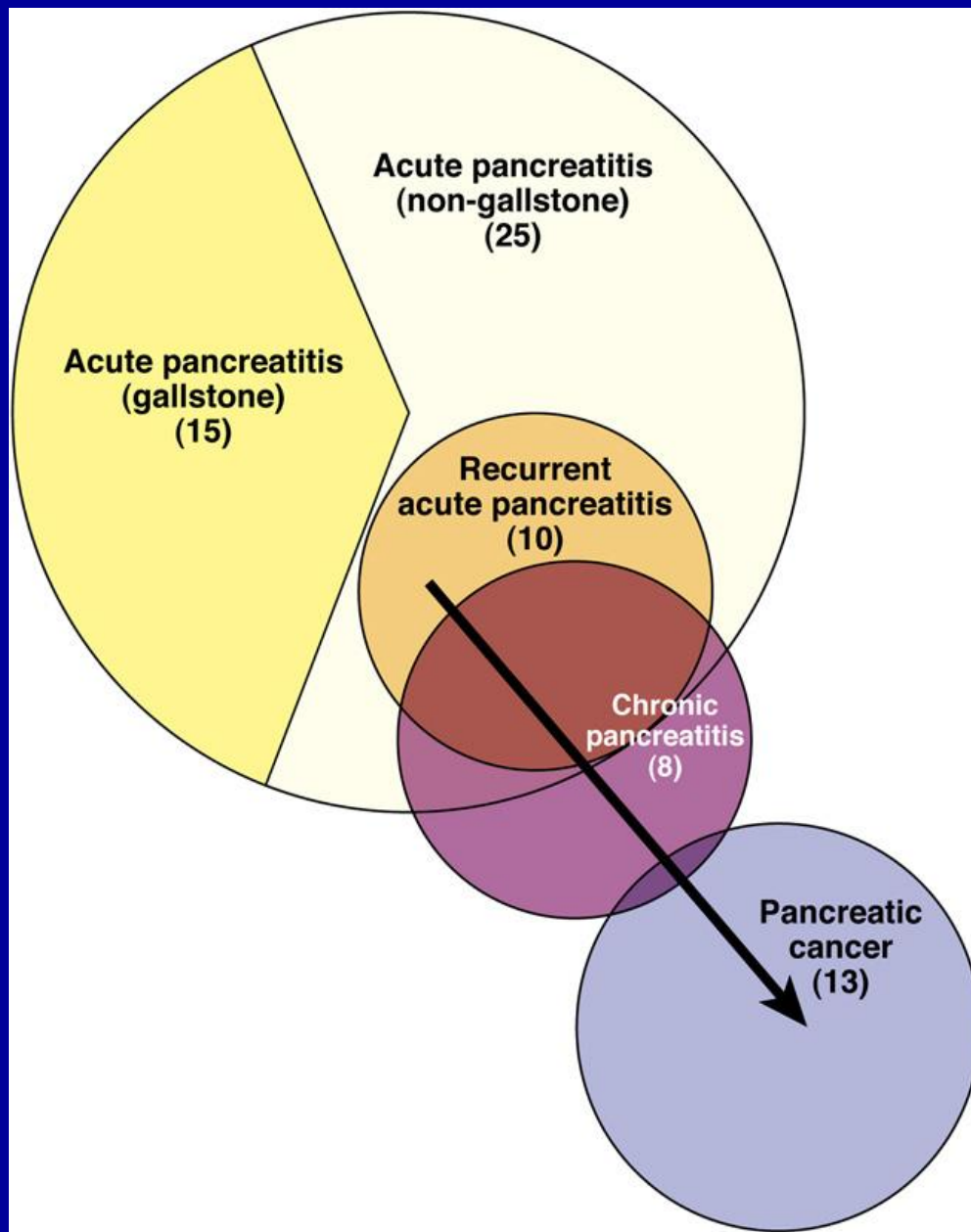
Diabetes duration, years	No. of studies	References	Relative risk 95%	Confidence interval
<1	3	34,42,49	5.38	3.49–8.30
1–4	5	34,42,49–51	1.95	1.65–2.31
5–9	4	34,49–51	1.49	1.05–2.12
>10	4	34,49–51	1.47	0.94–2.31
>1	14	12,15,30,32,34,35,37,40,46–51	1.96	1.60–2.40
>5	11	29,31,34,36,37,41,44,45,49–51	1.83	1.38–2.43

Pancreatic Cancer Risk Factors

Raimondi Best Practice Research & Gastroenterology 2010

Moderate (between 5 to 10 fold)

- Cystic Fibrosis
- Chronic Pancreatitis
 - The summary RR (95%CI) any PC diagnosed after 1 year from chronic pancreatitis diagnosis was 11.8 (5.8–24.1)
 - The summary RR (95%CI) any PC diagnosed within 2 years from chronic pancreatitis diagnosis was 5.8 (2.1–15.9)
 - Over a 20 year period, PC will develop in ~5% of all patients with chronic pancreatitis



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”

Five to 10% of PC related to hereditary factors

- Study from Louisiana (Falk et al. 1988)
 - Patients with pancreatic cancer
 - OR = 1.86 (1.42-2.44) any cancer
 - OR= 5.25 (2.08-13.21) with history of PC
- Study in French Canadians (Ghadirian et al. 1991)
 - 13-fold difference
 - 7.8% of PC patients with positive FH
 - 0.6% of controls with positive FH
- UPMC PAGER registry (unpublished data)
 - 619 PC cases
 - 33 with FDR: 5.3%
 - 50 with FDR or SDR: 8.1 %

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

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)*

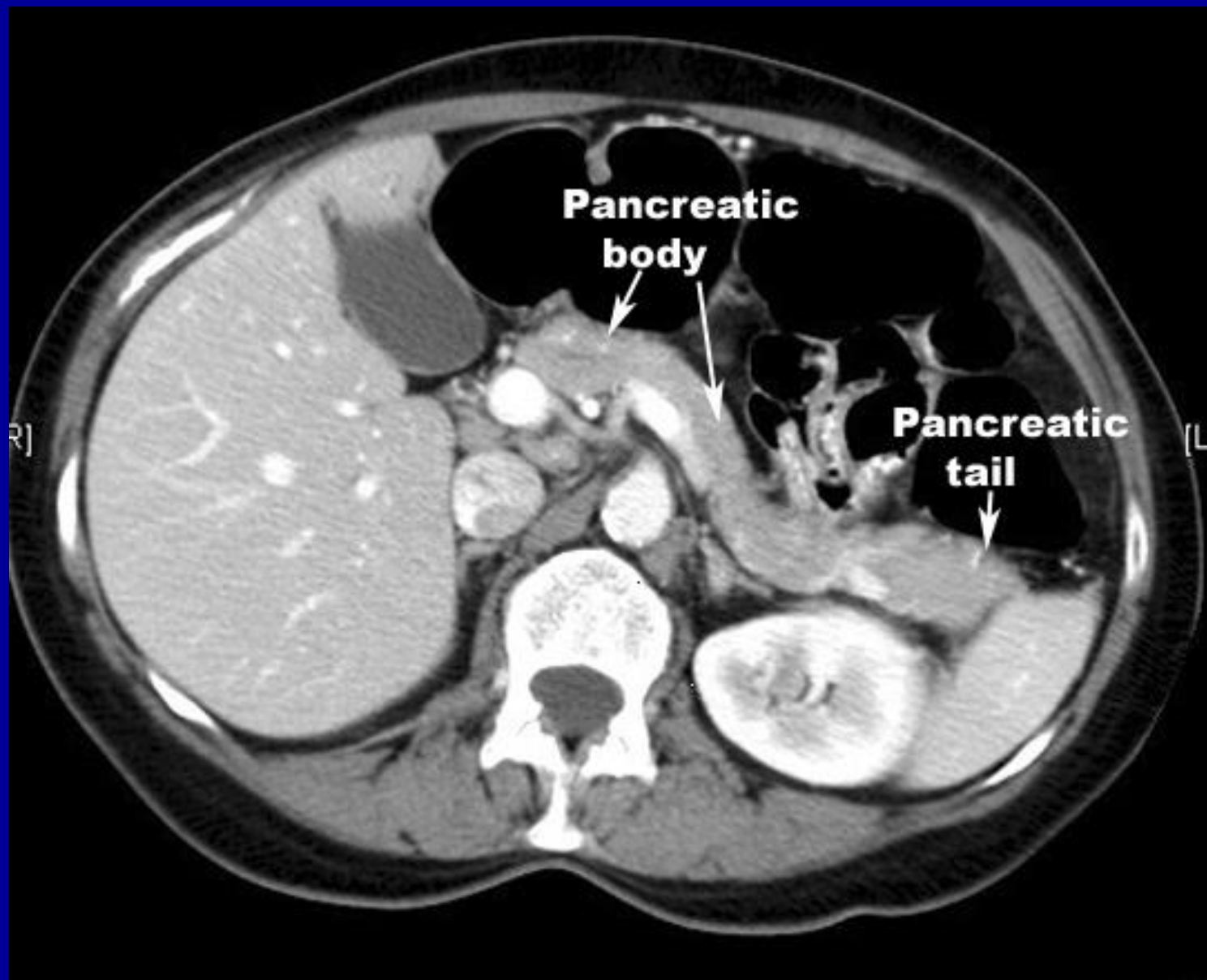
* $p < 0.005$

Definition of Cancer Screening

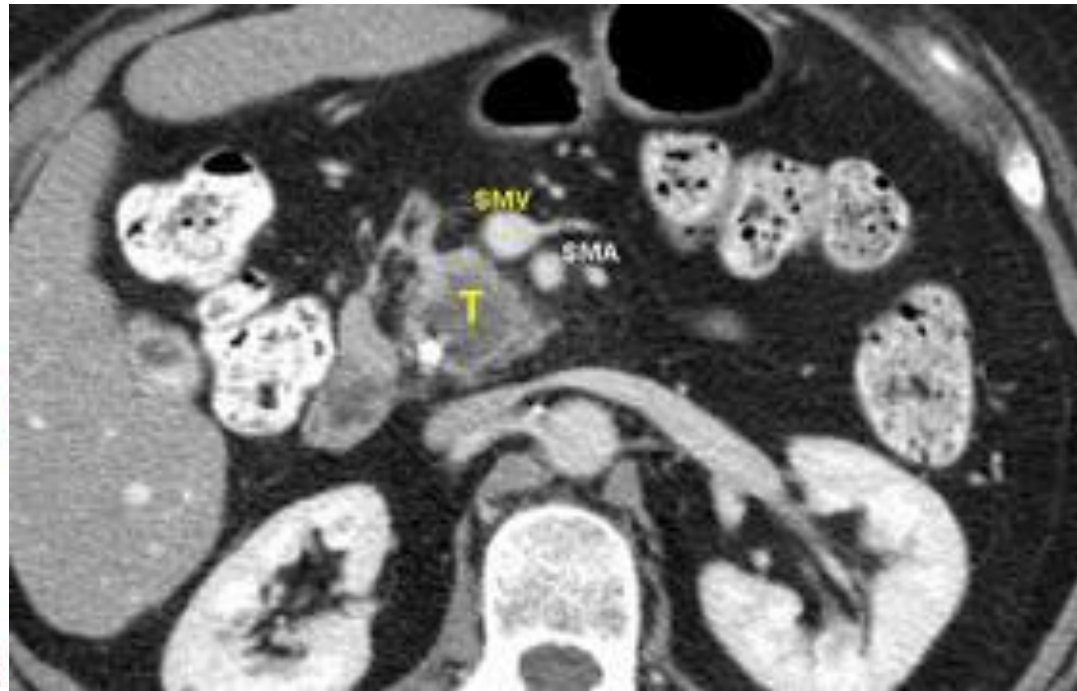
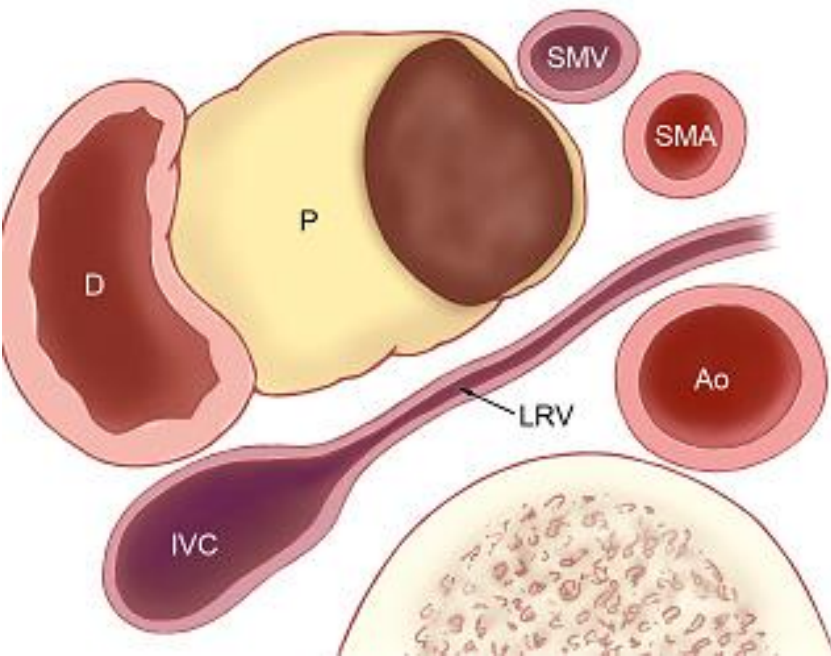
- **Surveillance:** Testing in asymptomatic high-risk individuals
- **Screening:** Testing in setting of asymptomatic general population
- **Diagnostic:** Testing in setting of symptoms

Imaging of the Pancreas

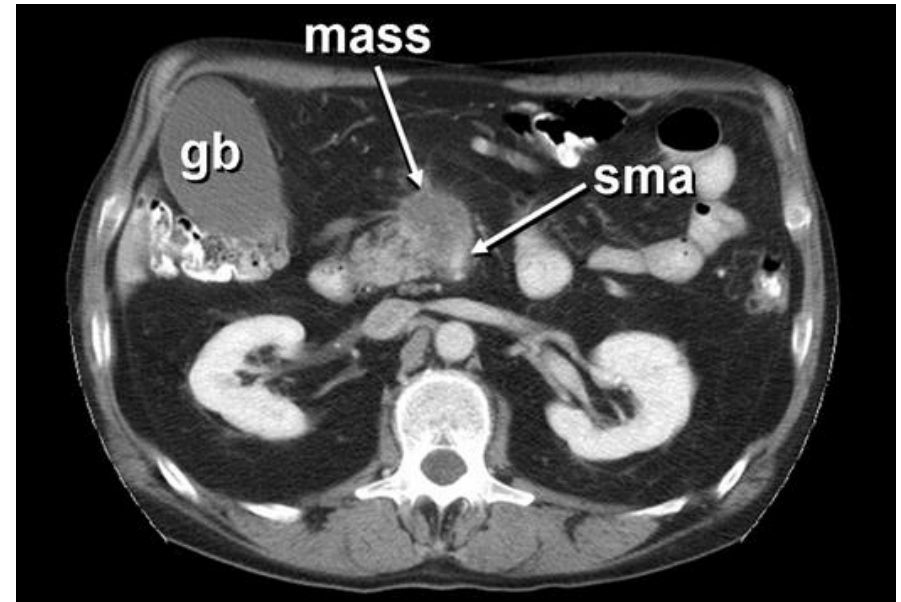
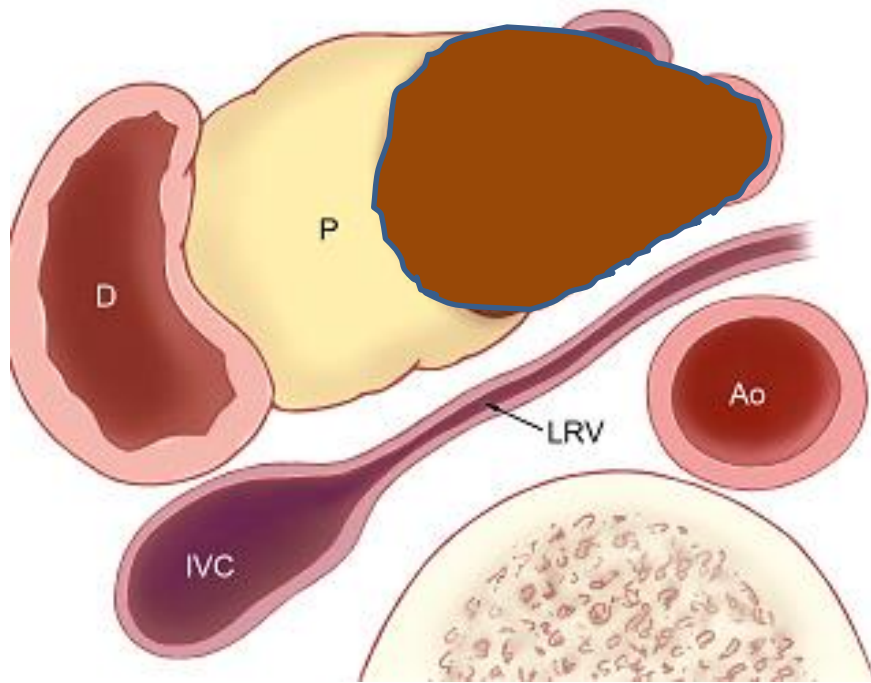
- Endoscopic ultrasound (EUS)
- Computed tomography (CT)
- Endoscopic Retrograde Cholangiopancreatography (ERCP)
- Magnetic resonance Cholangiopancreatography (MRCP)



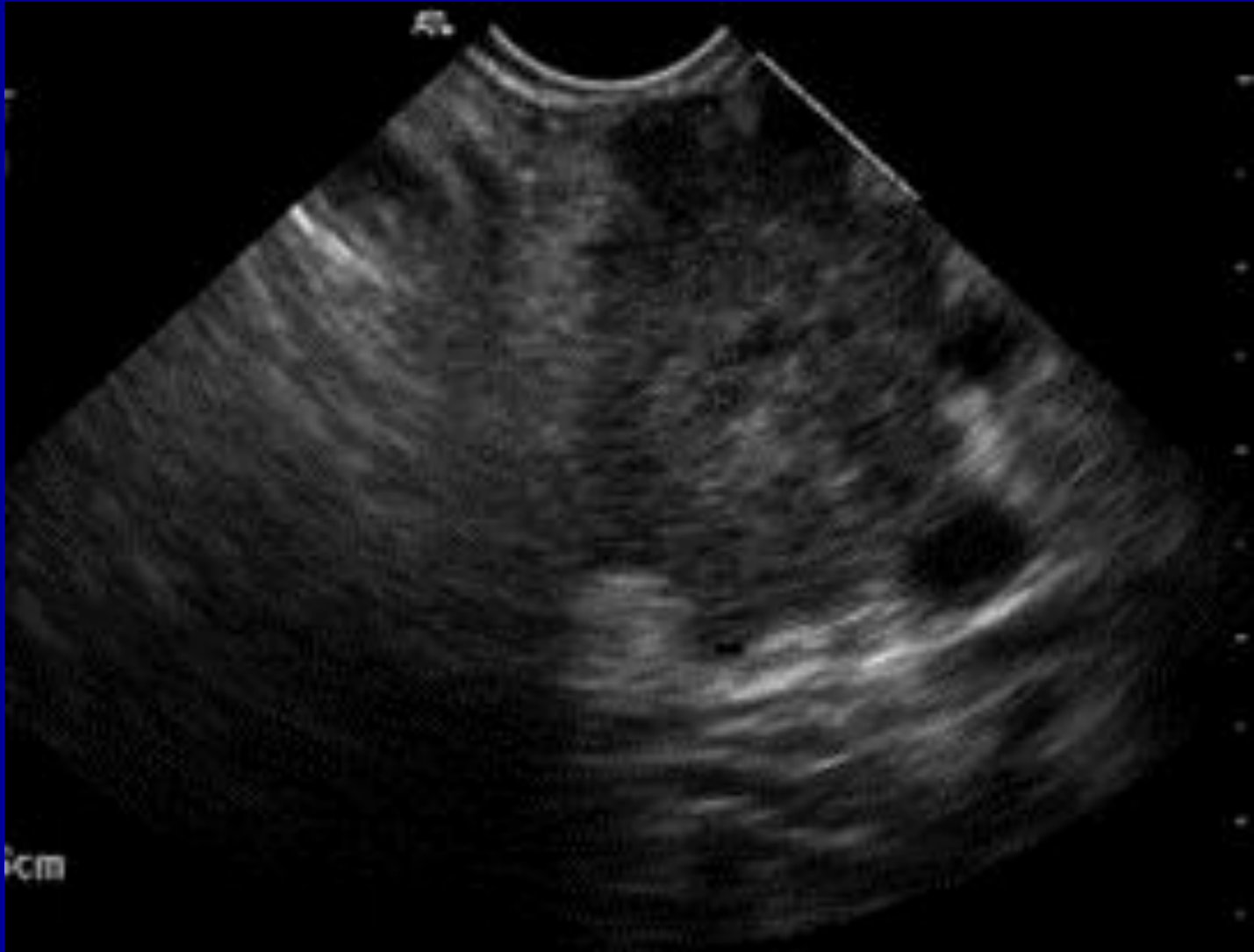
Clearly resectable disease...



vs. clearly **unresectable** disease



Endoscopic ultrasound (EUS)

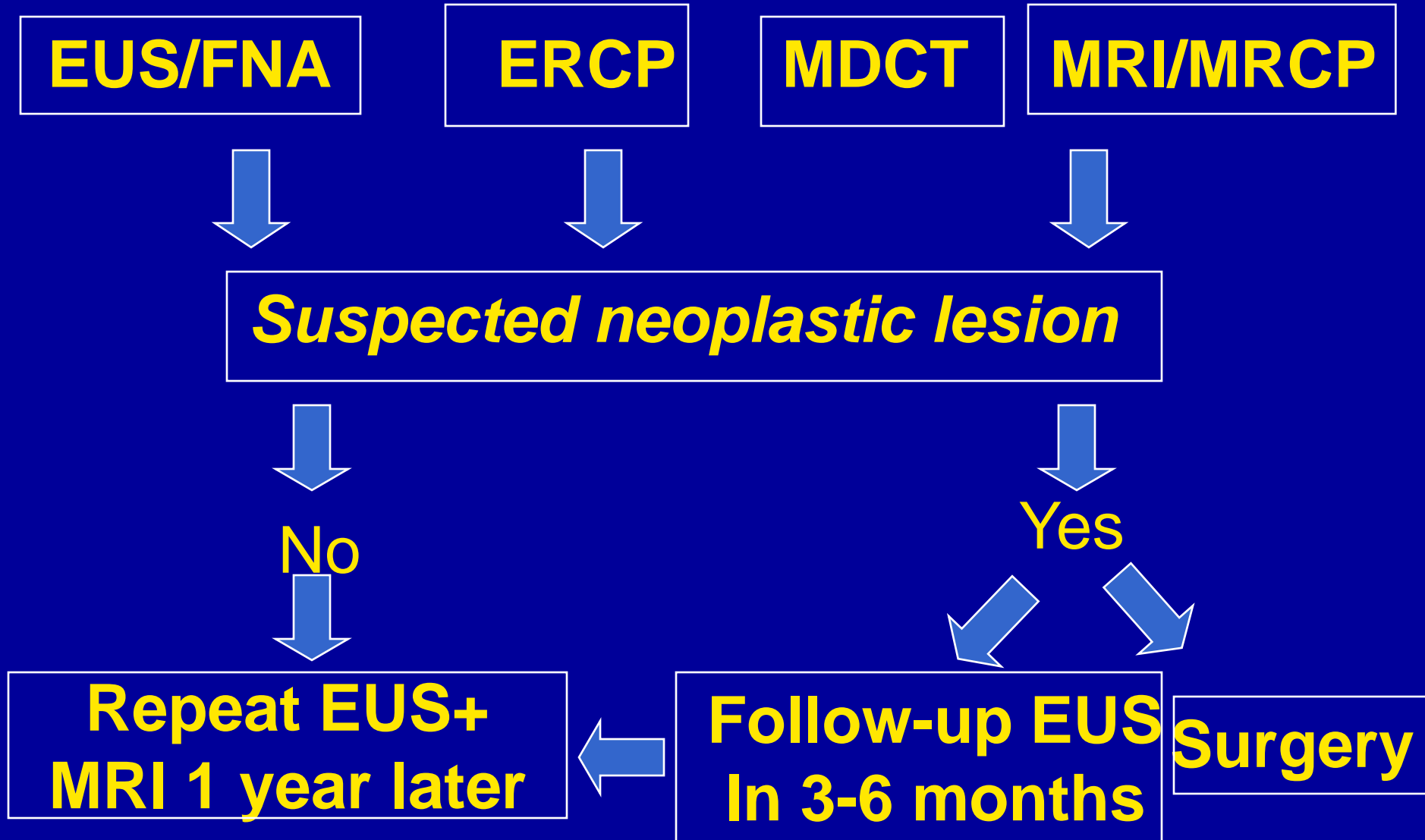


Endoscopic Retrograde Cholangiopancreatography (ERCP)





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%))

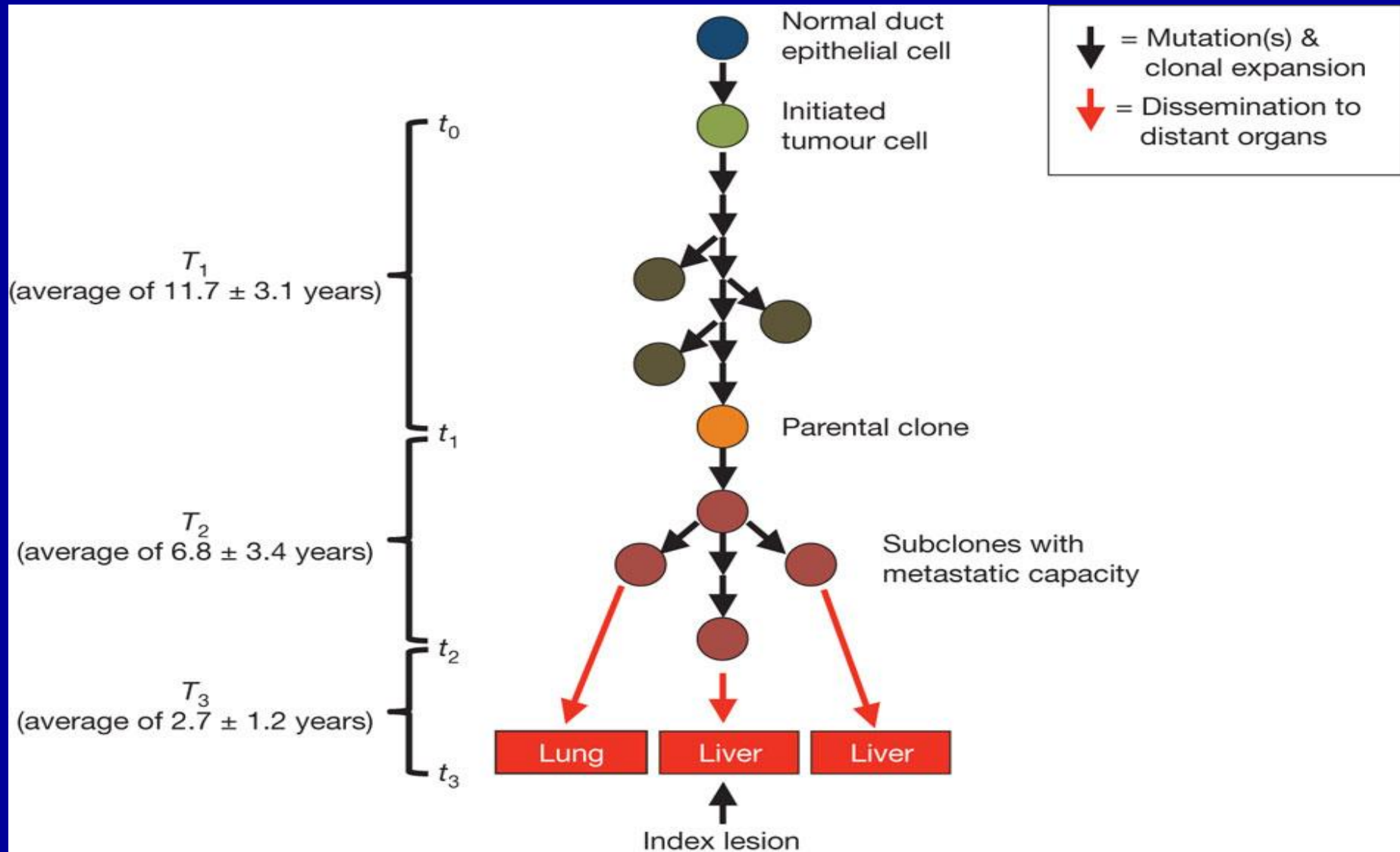
Can we screen the general population for PC?

- Screen 100,000 asymptomatic individuals
 - Age-adjusted incidence rate was 12.0 per 100,000 men and women per year*
- Apply a biomarker with a 100% sensitivity and 99% specificity
 - Detect all 12 PC cases
 - ~1,000 false positive studies
- Not feasible to screen population, must enrich

*Rates based on cases diagnosed in 2004-2008 from 17 SEER geographic areas

We need a cost effective strategy
to cull out approximately 25%
of the population that is at
highest risk for sporadic PDAC.
Then invasive testing may be
warranted.

Schema of the genetic evolution of pancreatic cancer





Thank you!