GENETIC RISK ASSESSMENT FOR THE EARLY DETECTION OF PANCREATIC CANCER

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Fay Kastrinos, MD, MPH

Director, Gastrointestinal Cancer Risk and Prevention Clinic
Director, Muzzi Mirza Pancreatic Cancer Prevention & Genetics Program

COLUMBIA UNIVERSITY
HERBERT IRVING COMPREHENSIVE CANCER CENTER

COLUMBIA

NewYork-Presbyterian

Outline

- Why the need to identify individuals at high-risk for pancreatic cancer?
  - Genetic testing as a risk stratification tool
- Family history of pancreatic cancer and germline pathogenic variants
- “Other” high-risk groups: Pancreatitis, Precursor lesions, i.e. IPMN
- Genetic testing as a risk stratification tool

Why the need to identify individuals at High-Risk for Pancreatic Cancer?

Pancreatic cancer is deadly

- 3rd leading cause of cancer death in the United States
- Only 10% undergo potentially curative surgery
- 5-year survival across all stages is approximately 11%

Improving pancreatic cancer related mortality relies on the detection and surgical resection of:

- An early-stage cancer, or
- A precursor lesion with high-grade dysplasia

Should we screen the general population?

Performance of a screening test

- Sensitivity and Specificity
- Positive Predictive Value (PPV)
  - Probability that individuals with a +screening test truly have disease
  - Depends on Prevalence of disease

Prevalence (%)	PPV+	Sensitivity	Specificity
0.1	1.8	90	95
1.0	15.4	90	95
5.0	48.6	90	95
50.0	94.7	90	95

General Population Screening for Pancreatic cancer?

- Screen 100,000 asymptomatic individuals
- 12 individuals per 100,000
- Apply a biomarker with a 100% sensitivity and 99% specificity

	Pancreatic Cancer	NO Pancreatic Cancer	PPV=1.2%
Test Positive	12	1,000	1,012
Test Negative	0	98,988	98,988
	12	99,988	100,000

Enrich the population to justify screening

Select populations with an increased prevalence of pancreatic cancer

High Risk Populations

- Family history of pancreatic cancer
- Precursor lesions of the pancreas
- New Onset Diabetes

Family history of Pancreatic Cancer

~10% of pancreatic cancer cases have a family history of cancer

- Genetic Predisposition: having a known pathogenic variant in the family
- Familial Aggregation

Incidence of Pancreatic Cancer based on # of affected First-Degree Relatives

# of First-degree relatives	Standardized Incidence Ratio	Incidence (per 100,000)
General US population	-	9
1	4.5x	41
2	6.4x	58
≥3	32.0x	288

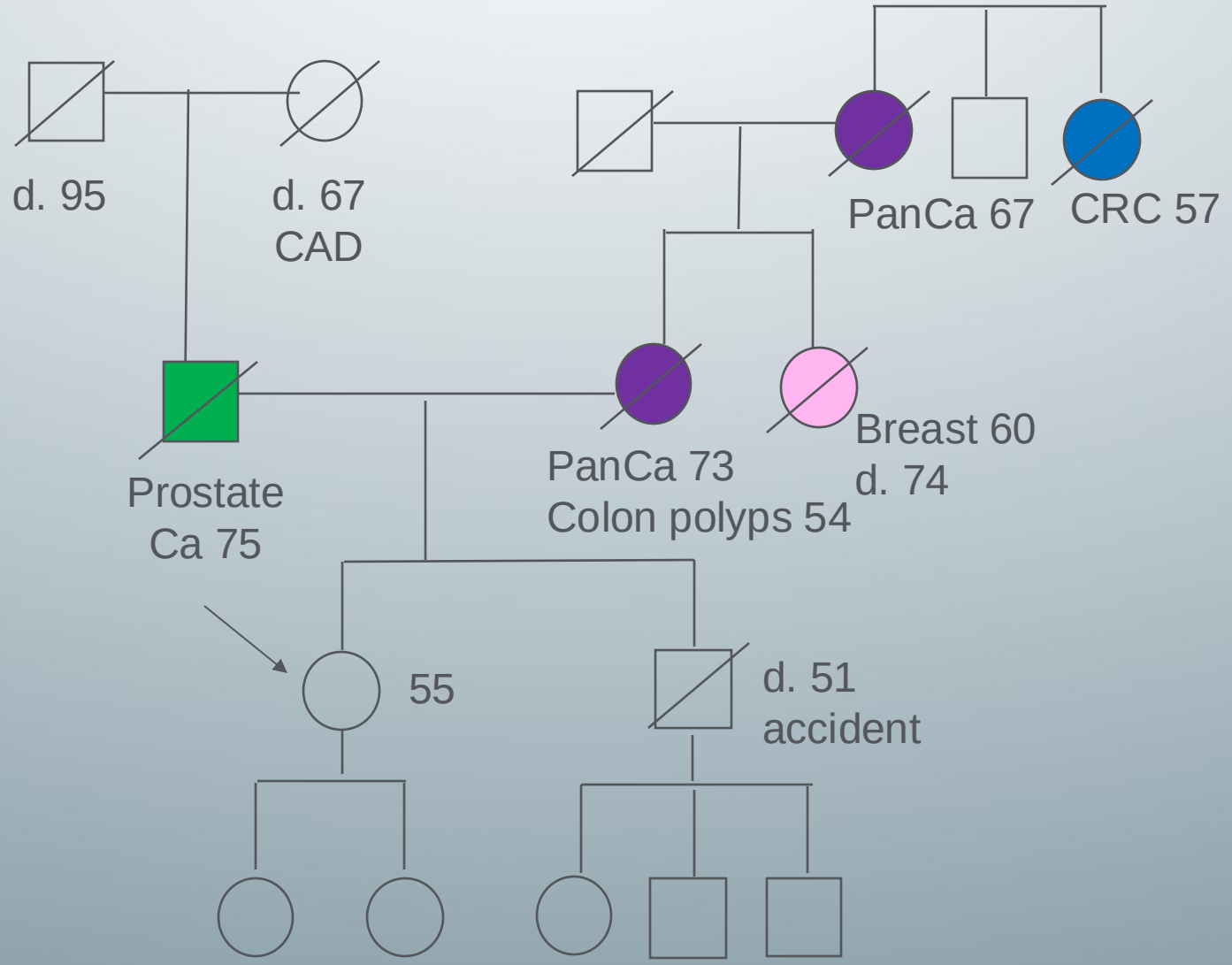
Klein A. Cancer Research 2004

Definition of a Familial Pancreatic Cancer Kindred

Family with ≥2 relatives with pancreatic cancer

- Two of the individuals have a first-degree relationship to each other (parent-child, parent-sibling)

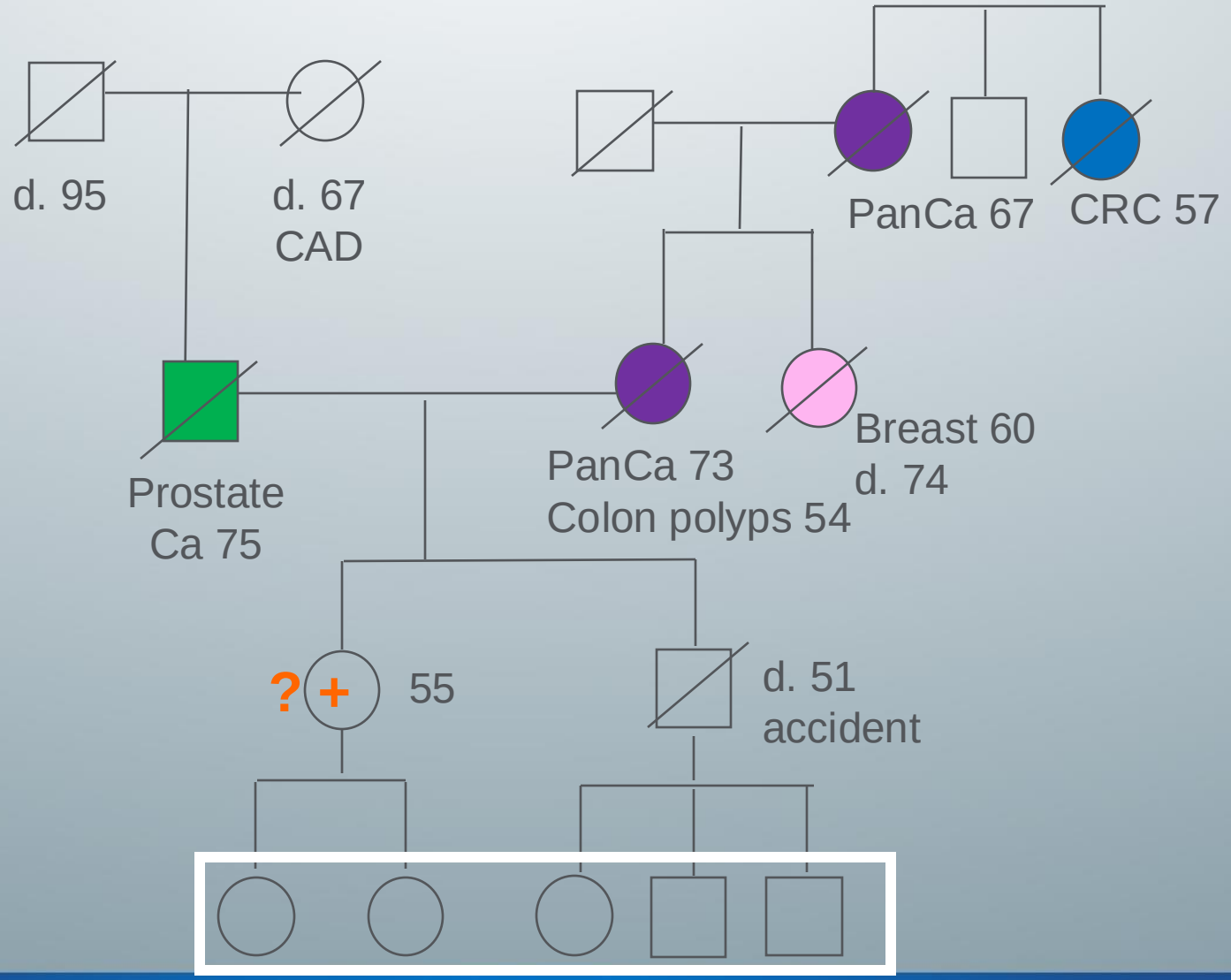
FAMILIAL PANCREATIC CANCER



Familial Pancreatic Cancer

- Surveillance eligible
- Offer GENETIC TESTING!

Familial Pancreatic Cancer



Association between Inherited Germline Mutations and Pancreatic Cancer

Methods

- 3,030 PDAC cases at Mayo Clinic:2000-2016
- Controls: the Genome Aggregation Database (n=123,136) and Exome Aggregation Consortium (n=53,105)
- 21 candidate genes

Results

- Prevalence of mutations in unselected PDAC cases: 8.2%
- 6 genes significantly associated with PDAC
- Prevalence of mutations in the 6 genes: 5.5% in unselected cases; 7.9% with family history of PDAC

Hu et al, JAMA. 2018

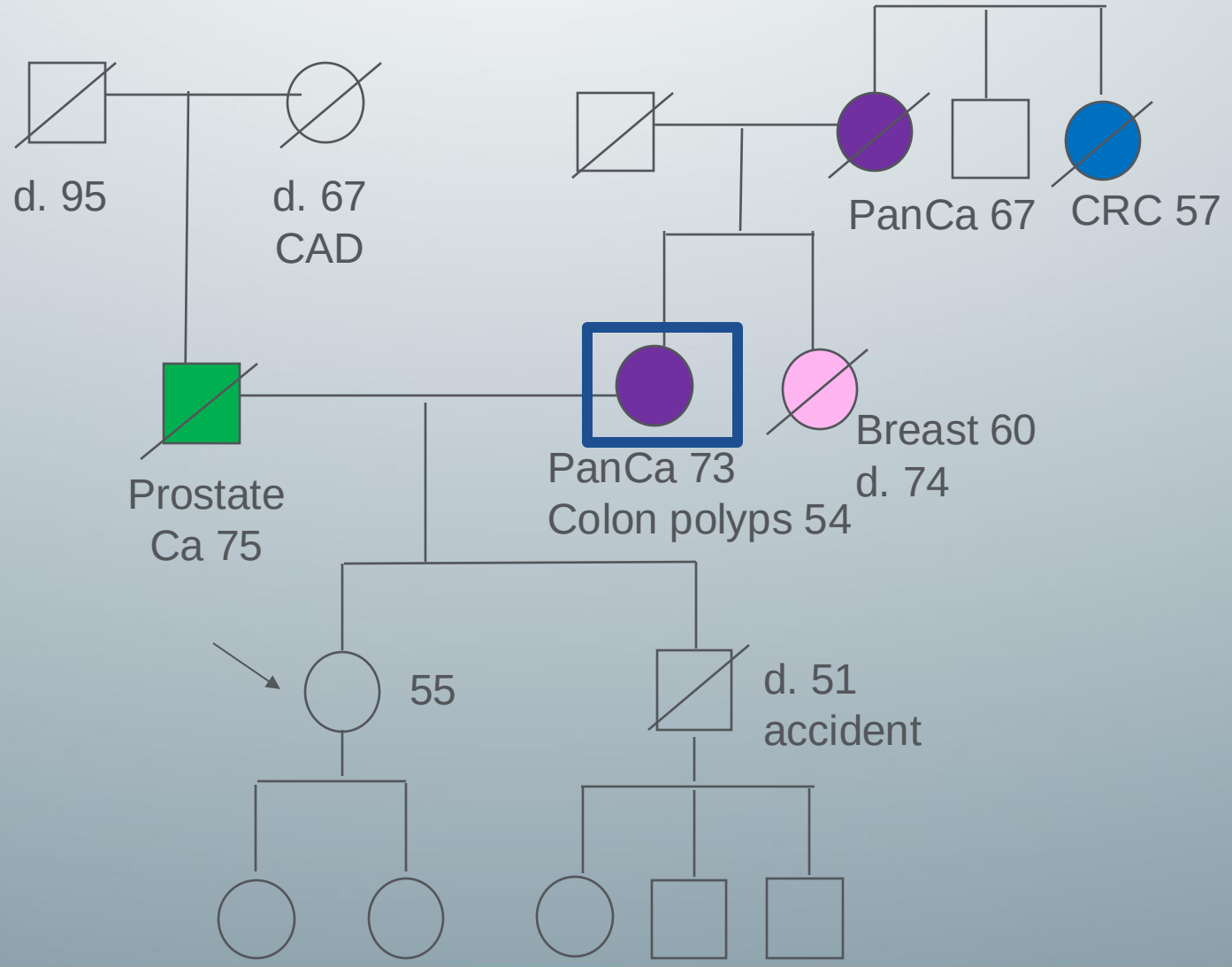
INHERITED GERMLINE MUTATIONS AND PANCREATIC CANCER

Table 3. Comparisons of Mutation Carriers by Panel Gene Between Pancreatic Cancer Cases and gnomAD Controls

Genes	Cases			gnomAD Controls			Cancer Risk[a]	
	Cases With Mutations, No.	Individuals Tested, No.[b]	Carrier Frequency, %	Controls With Mutations, No.	Individuals Tested, No.	Carrier Frequency, %	Odds Ratio (95% CI)	Adjusted *P* Value[c]
Genes Significantly Associated With Pancreatic Cancer								
CDKN2A	9	2999	0.30	15	99 493	0.02	12.33 (5.43-25.61)	<.001
TP53	6	2999	0.20	25	104 162	0.02	6.70 (2.52-14.95)	<.001
MLH1	4	2999	0.13	25	103 526	0.02	6.66 (1.94-17.53)	.01
BRCA2	57	2999	1.90	313	102 739	0.30	6.20 (4.62-8.17)	<.001
ATM	69	2999	2.30	386	104 016	0.37	5.71 (4.38-7.33)	<.001
BRCA1	18	2999	0.60	208	104 122	0.20	2.58 (1.54-4.05)	.002
Genes Not Significantly Associated With Pancreatic Cancer								
NF1	4	2999	0.13	31	103 812	0.03	3.70 (1.11-9.22)	.25
PALB2	12	2999	0.40	153	104 169	0.15	2.33 (1.23-4.01)	.09
CDH1	1	2999	0.03	15	102 110	0.01	2.30 (0.13-11.39)	>.99
MSH6	6	2999	0.20	101	102 802	0.10	1.98 (0.77-4.14)	>.99
FANCC	8	2999	0.27	129	104 042	0.12	1.69 (0.76-3.21)	>.99
MSH2	1	2999	0.03	16	103 327	0.02	1.58 (0.09-7.54)	>.99
BARD1	4	2999	0.13	86	102 189	0.08	1.32 (0.40-3.15)	>.99
CHEK2	33	2999	1.10	572	102 856	0.56	1.31 (0.91-1.83)	>.99
RAD51C	3	2999	0.10	94	104 128	0.09	1.11 (0.27-2.97)	>.99
NBN	4	2999	0.13	125	103 912	0.12	0.86 (0.27-2.04)	>.99
BRIP1	4	2999	0.13	194	104 071	0.19	0.78 (0.28-1.71)	>.99
MRE11A	2	2999	0.07	96	104 071	0.09	0.71 (0.12-2.23)	>.99
PMS2	2	2999	0.07	86	101 976	0.08	0.70 (0.12-2.22)	>.99

Abbreviation: gnomAD, Genome Aggregation Database.

Familial Pancreatic Cancer



NCCN Guidelines Version 2024

TESTING CRITERIA FOR PANCREATIC CANCER SUSCEPTIBILITY GENES[a]

DIAGNOSIS	TESTING CRITERIA
Exocrine pancreatic cancers	Recommend genetic counseling and germline testing[m] for • All individuals diagnosed with exocrine pancreatic cancer[n] • First-degree relatives of individuals diagnosed with exocrine pancreatic cancer[o]

- Multi-gene panel testing
  - Genes that are typically tested for include *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, Lynch syndrome genes, *PALB2*, *STK11*, and *TP53*

Inherited Cancer Syndrome	Affected Genes	Relative Risk
Hereditary Breast and Ovarian Cancer (HBOC)*	*BRCA1, BRCA2*	2-10
Non-HBOC	*PALB2*	increased
Lynch Syndrome	*MLH1, MSH2, MSH6, PMS2*	8
Familial Atypical Mole Melanoma (FAMMM)	*CDKN2A (p16)*	13-22
Peutz-Jeghers Syndrome (PJS)	*STK11/LKB1*	132
Ataxia Telangiectasia	*ATM*	2.7-5
Hereditary Pancreatitis	*PRSS1, SPINK, CTRC, CFTR*	26-60

Inherited Cancer Syndromes: Estimated Lifetime Risk of ~10%

- **FAMMM (*p16/CDKN2A**), *BRCA2*, or *PALB2* mutation**
- At 50 years or 10 years younger than the youngest relative with pancreatic cancer; *CDKN2A* begin at 40 years*
- ≥1 pancreatic cancer cases in the family* who is a FDR or SDR of the eligible subject

Inherited Cancer Syndromes: Estimated Lifetime Risk of ~5%

- ***BRCA1*, *ATM*, Lynch syndrome (*MLH1, MSH2, MSH6, PMS2*)**
- At 55* years or 10 years younger than the youngest relative with pancreatic cancer
- ≥1 pancreatic cancer cases in the family who is a FDR or SDR of the eligible subject

Inherited cancer syndromes

- Peutz-Jeghers Syndrome
  - At least 30 years old
  - *STK11* gene mutation carrier

- Hereditary Pancreatitis
  - Gene mutations that predispose to chronic pancreatitis:
    - *PRSS1, SPINK, CFTR, CTRC*
  - At 40 years or 20 years since first attack of pancreatitis

Hereditary Pancreatitis

- Multi-gene panel includes *PRSS1*, *SPINK1*, *CFTR*, and *CTRC*

- Limitations of multi-gene panels involve complex interpretations of results:
  - Isolated mutations in genes other than *PRSS1* are insufficient to cause pancreatitis
  - The majority of individuals with a single mutation do not have pancreatitis
  - These variants are a risk factor but additional modifying factors also contribute
  - Variants of uncertain significance are common

Pancreatic Cancer in Hereditary Pancreatitis

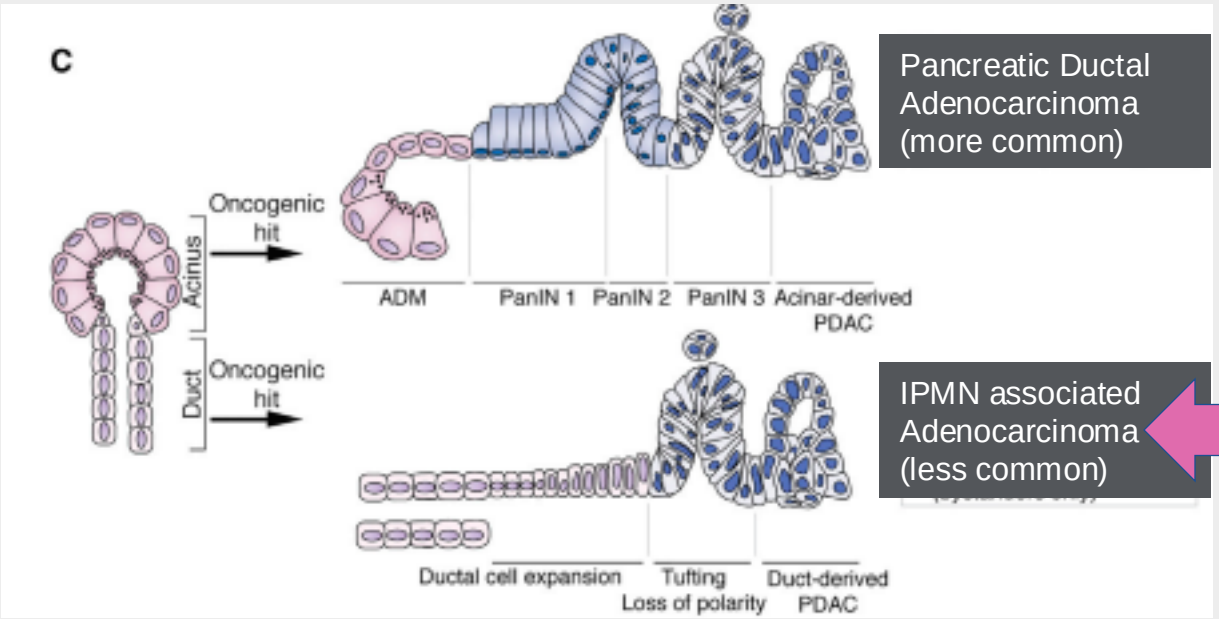
- Earlier studies estimated risk of pancreatic cancer at ~40%
  - Overestimate due to inclusion of smokers
  - For non-smokers the lifetime risk ~20%
- Onset of chronic pancreatitis is 20-30 years earlier than in sporadic
- Special consideration in *PRSS1* carriers: Total pancreatectomy with islet autotransplantation
  - For carriers with severe manifestations of pancreatitis
  - Consider minimizing alternative surgeries (partial pancreatectomy, lateral pancreaticojejunostomy) to preserve islet cell mass

Indications for Genetic Testing in Pancreatitis

Molecular genetic testing may be considered *in any individual with pancreatitis and any one of the following*:

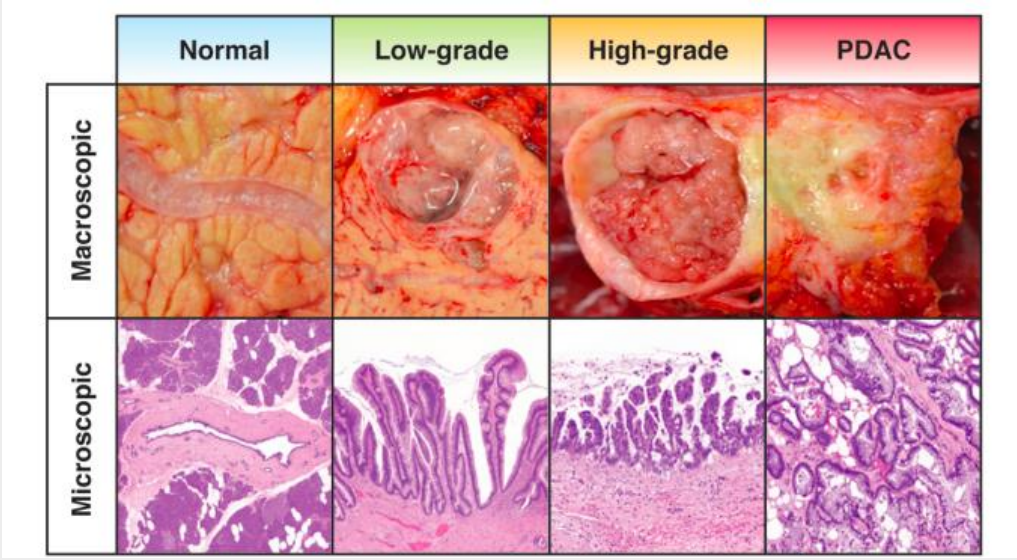
- Unexplained acute pancreatitis in childhood
- Recurrent acute pancreatitis (RAP) of unknown cause
- Chronic pancreatitis of unknown cause, particularly with onset <25 years
- Family history of at least one relative with RAP, chronic pancreatitis of unknown cause, or childhood pancreatitis of unknown cause

Individuals with Precursor Lesions: Targets for Early Detection of Pancreatic Cancer



Intraductal Papillary Mucinous Neoplasia (IPMN)

- Detected in ~15% of asymptomatic individuals with abdominal MRI
- 3 types: Main pancreatic duct (MD; 10-35%) versus branch duct (BD; 40-65%) versus mixed (15-40%)



•Among resected IPMNs:

•HGD in 62% of MD, 24% of BD and 58% of mixed type
•Pancreatic cancer in 44% of MD, 24% of BD, and 45% of mixed type

Singhi AD. Gastroenterology 2019

Genetic testing for precursor lesions

- Consider genetic testing as a risk stratification tool
  - Particularly if +family history of cancer

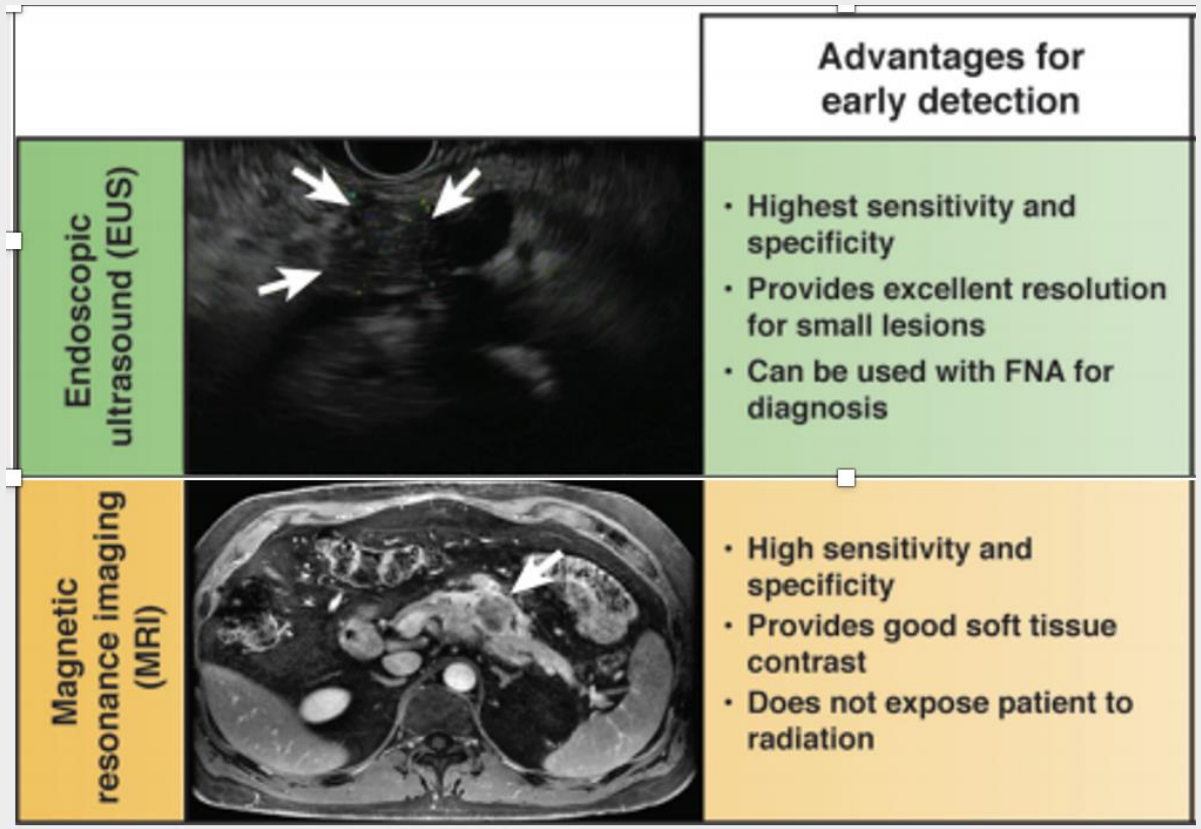
- Current surveillance intervals for IPMN vary
  - Based on location, size, features of cyst

- Identified mutation carriers with IPMN:
  - Surveillance different than if gene negative
  - Importance of cascade testing

Success of a Screening Program for High-Risk Individuals

- Resectable carcinoma
  - Detection and treatment of T1N0M0
- Detection and treatment of PanIN-3
- Detection and treatment of IPMN with high grade dysplasia

Imaging the Pancreas in High-Risk Individuals



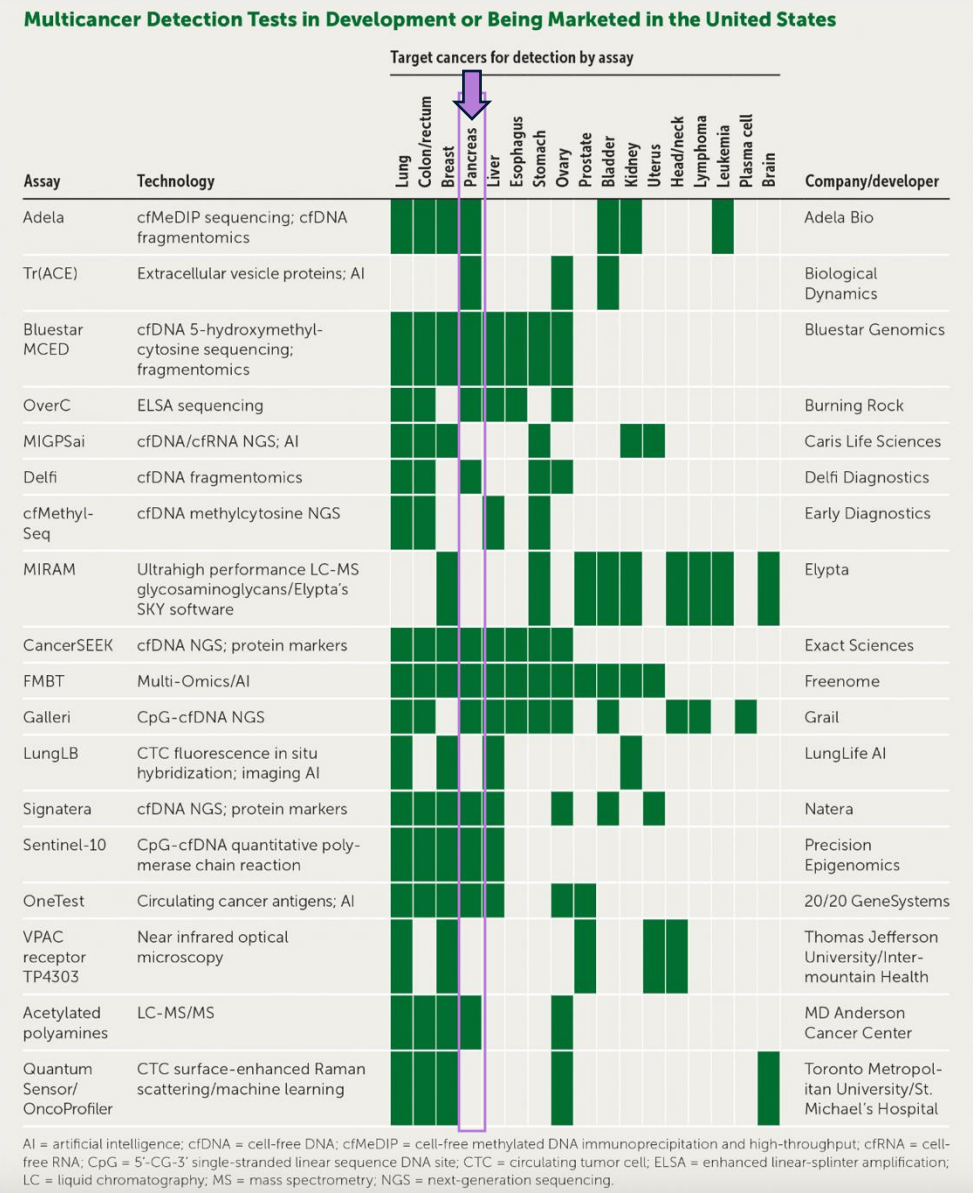
- CAPS Screening Program
- 17731 HRI (1998-2021) under surveillance
  - 26 HRI developed PDAC
- **HRI** versus Controls:
  - **Smaller tumor size**: 2.5 vs 3.6 cm
  - **Diagnosed with a lower stage**
    - Stage I, 10 [38.5%] vs 155 [10.3%]
    - Stage II, 8 [30.8%] vs 377 [25.1%]
  - **Better 5-yr mortality**: 43% vs 86%; HR, 3.6
  - **Longer Survival**: median OS, 61.7 vs 8.0 months;
    - 5-year OS rate, 50% vs 9%

Blackford AL, et al. JAMA Oncol 2024

Challenges of a Surveillance Program

- Pancreatic imaging cannot grade dysplasia in the pancreas
- Patients have years of normal imaging
  - How to further risk stratify
- Follow-up of benign and stable findings
  - SB-IPMNs
- Incidental findings
- Continued subject participation

Non-Invasive Screening: MCED and SCED Testing



Multicancer Detection Tests in Development or Being Marketed in the United States

Assay	Technology	Target cancers for detection by assay: Lung	Colon/rectum	Breast	Pancreas	Liver	Esophagus	Stomach	Ovary	Prostate	Bladder	Kidney	Uterus	Head/neck	Lymphoma	Leukemia	Plasma cell	Brain	Company/developer
Adela	cfMeDIP sequencing; cfDNA fragmentomics	■	■	■	■						■	■				■			Adela Bio
Tr(ACE)	Extracellular vesicle proteins; AI				■				■		■								Biological Dynamics
Bluestar MCED	cfDNA 5-hydroxymethyl-cytosine sequencing; fragmentomics	■	■	■	■	■	■	■	■										Bluestar Genomics
OverC	ELSA sequencing	■	■		■	■	■		■										Burning Rock
MIGPSai	cfDNA/cfRNA NGS; AI	■	■	■				■				■	■						Caris Life Sciences
Delfi	cfDNA fragmentomics	■	■		■			■	■										Delfi Diagnostics
cfMethyl-Seq	cfDNA methylcytosine NGS	■	■			■		■											Early Diagnostics
MIRAM	Ultrahigh performance LC-MS glycosaminoglycans/Elypta's SKY software			■				■		■	■	■		■	■	■		■	Elypta
CancerSEEK	cfDNA NGS; protein markers	■	■	■	■	■	■	■	■										Exact Sciences
FMBT	Multi-Omics/AI	■	■	■	■	■	■	■	■	■	■	■							Freenome
Galleri	CpG-cfDNA NGS	■	■		■	■	■	■	■		■			■	■		■		Grail
LungLB	CTC fluorescence in situ hybridization; imaging AI	■		■		■						■							LungLife AI
Signatera	cfDNA NGS; protein markers	■	■	■	■	■			■		■		■						Natera
Sentinel-10	CpG-cfDNA quantitative polymerase chain reaction	■	■	■	■	■													Precision Epigenomics
OneTest	Circulating cancer antigens; AI	■	■	■	■	■			■	■									20/20 GeneSystems
VPAC receptor TP4303	Near infrared optical microscopy	■		■						■			■	■					Thomas Jefferson University/Intermountain Health
Acetylated polyamines	LC-MS/MS	■	■	■	■				■										MD Anderson Cancer Center
Quantum Sensor/ OncoProfiler	CTC surface-enhanced Raman scattering/machine learning	■	■	■					■									■	Toronto Metropolitan University/St. Michael's Hospital

AI = artificial intelligence; cfDNA = cell-free DNA; cfMeDIP = cell-free methylated DNA immunoprecipitation and high-throughput; cfRNA = cell-free RNA; CpG = 5'-CG-3' single-stranded linear sequence DNA site; CTC = circulating tumor cell; ELSA = enhanced linear-splinter amplification; LC = liquid chromatography; MS = mass spectrometry; NGS = next-generation sequencing.

Doubeni CA, et al. *Am Fam Physician.* 2023

- Pathfinder study: Galleri test
  - Supports feasibility
- Cancer signal detected in 92 (1.4%) of 6621 subjects
- Overall sensitivity PDAC: 83.7%
  - 61.9% for stage I
  - 60.0% for stage II
  - 85.7% stage III
  - 95.9% stage IV

Schrag, D, et al. *Lancet*. 2023

Examples of Single-Cancer Early Detection (SCED) Tests for PDAC

- Methylation-based markers
- Protein-based markers
- Exosome-based with miRNA

Avantect Pancreatic Cancer Test

Leverages the 5-hydroxymethylcytosine signatures in cfDNA

- A stable epigenetic marker for early detection
- Arises as the first step of active demethylation of the cytosine base in DNA by translocation enzymes, marking regions of active transcription and gene regulation

Performance in an independent case-control patient cohort (n=2,150)

- PDAC in 102, No PDAC in 2,048

	Sensitivity	Specificty
Early-stage (I/II)	68.3%	96.9%

New Algorithm: Avantect + CA19-9 + Genetic Modifiers

- Anticipated increase in Sensitivity without loss of Specificity

Haan et al. Clin Gastro Hep, 2023

Immunov-2: Next-generation testing of Multiplex Blood Protein Biomarker Test (Model Development)

- Only 1 SCED test, IMMray PanCan-d, assessed in HRI
  - A multi-analyte test with CA19-9 and 8 other biomarkers
  - First commercially available SCED for PDAC

Population	Population, n	Controls, n	Cases, n	Spe., % (95% CI)	Sen., % (95% CI)	AUC
Whole population	**623**	**495**	**128**	**98 (96-99)**	**85 (79-91)**	**0.945**
Low CA19-9	525	480	45	98 (96-99)	60 (46-74)	0.861
High CA19-9	98	15	83	93 (68-100)**	99 (93-100)	0.949
Male*	241	175	66	97 (94-99)	86 (78-95)	0.944
Female*	370	320	50	98 (97-100)	86 (76-96)	0.940
Cystic lesion	178	178	-	97 (6 FP, 172 TN)	NA	NA
Stage 1	583	495	88	98 (96-99)	84 (76-92)	0.941
Stage 2	535	495	40	98 (96-99)	88 (77-98)	0.953
Diabetes	91	48	43	96 (90-100) ***	91 (82-99)	0.942
Age >=65	294	214	80	98 (96-100)	91 (85-97)	0.967

CLARITI Validation in HRI: Case-control, multi-center study with aim of 184 cases, 736 controls

Palma NA, et al. CGA-IGC 2024

Exosome-based transcriptomic signature for Early Detection of PDAC

- Tumor-derived exosomal cargo, particularly microRNAs, as cancer-specific biomarkers
- Exosomes retain cytoplasmic content of the derived cell and biology of the tissue of origin
- Panel of 5 cf- and 8 exo-miRNAs

	All stage	Early-stage (I/II)	Identified CA19-9 negative cases (<37U/ml)	Combined with CA19-9
AUC	0.98 (training); 0.93 (validation)	0.93	0.96	0.99 vs 0.86 CA19-9 alone

Nakamura et al. Gastroenterology 2022

- An investigational exosome-based liquid biopsy + CA19-9*
  - Detected 97% of Stage I to II PDACs
  - Limitation: lack of miRNA control against which to normalize the levels of candidate microRNAs used to develop the signature

*AACR Annual meeting, 2024; Abstract 3899

Potential Integration of SCED tests in Surveillance Protocols for HRI

- Combine SCED with routine imaging
  - Alternating circulating blood test and imaging test every 6 months
    - Potential to capture interval cancers
    - +SCED: direct EUS (+/- MRI/MRCP)

- SCED as a potential risk stratification tool
  - Can SCED results be used to triage HRI for less intensive imaging?
  - Ie. populations: no family history of PDAC, younger ages being screened

Conclusions

- General Population screening for pancreatic cancer not indicated
- Enriched populations for ‘Screening’
  - High risk individuals: Gene mutation carriers & FPC kindreds
  - Collaborative efforts needed
  - Biomarker validation for further risk stratification
- Use of genetic testing in families with pancreatic cancer or precursor lesions and pancreatitis is a valuable risk assessment tool

Thank you

fk18@Columbia.edu

COLUMBIA UNIVERSITY
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