

Pancreas Cancer Genomics

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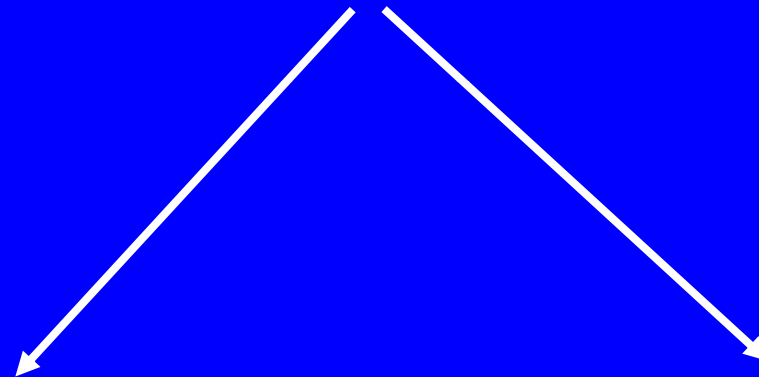
Samuel Lunenfeld Research Institute

Mount Sinai Hospital

University of Toronto

Fate of the Next 100 Pancreas Cancer Patients

100 Pancreas Cancer Patients



15-20

80-85

Operable

Not Operable



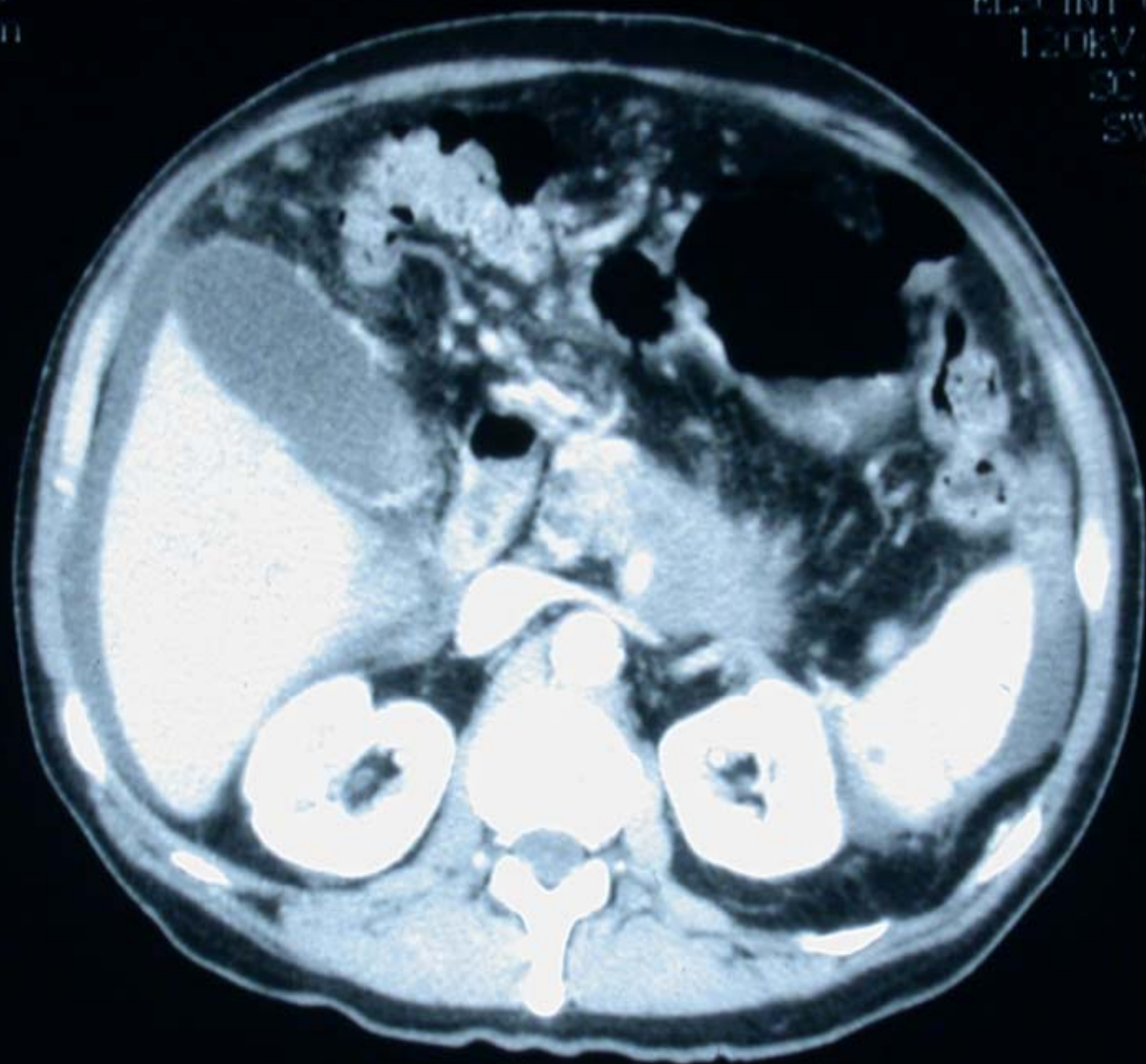
2-3 Five Year Survivors

1445-25
2180mm

21 Apr 97 16:15:11
ELSCINT CT TWIN
120KV, 333mAs
SC 430mm
SW 5.5mm
ST 31.1s
Z 120

C

ABDO +C



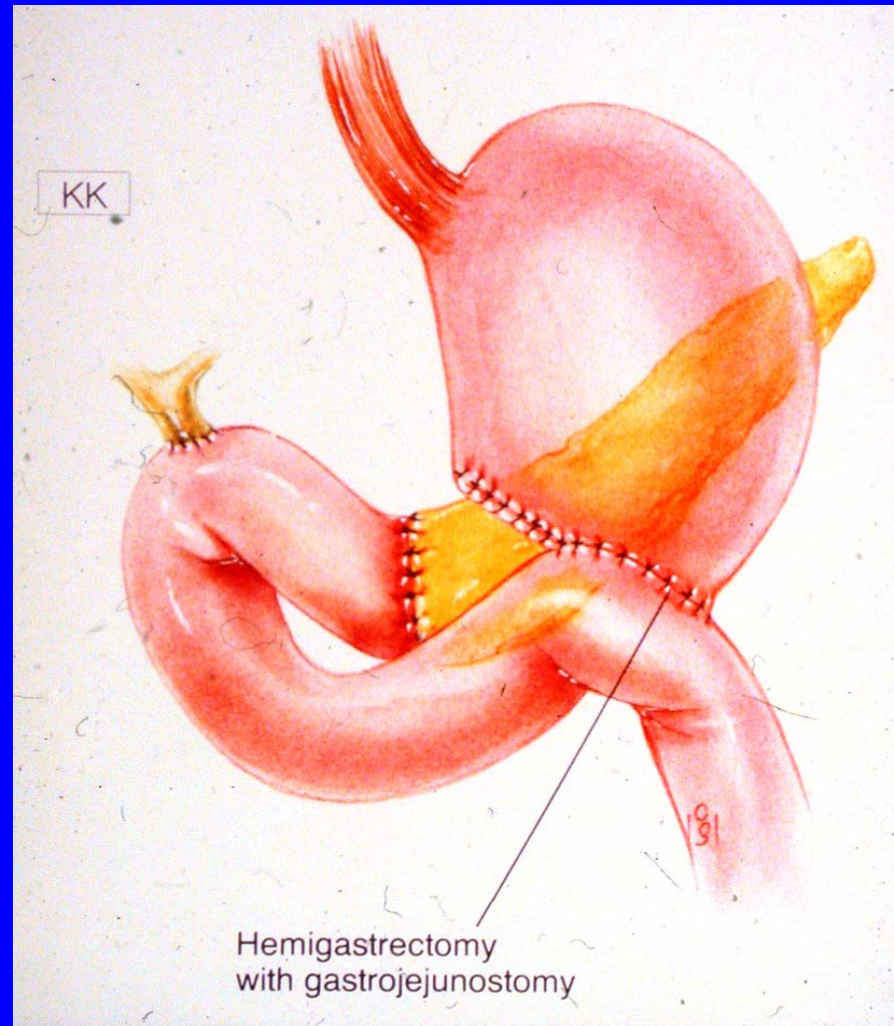
10
cm

R

L

C1 40
U1 400

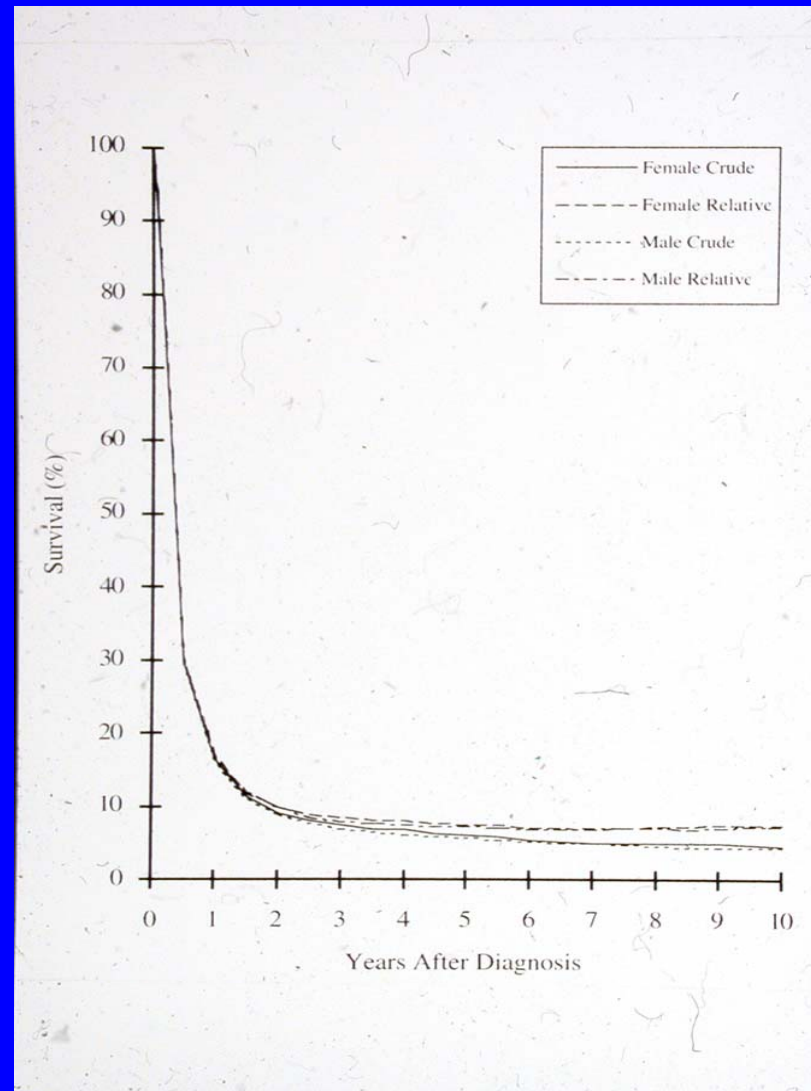
Whipple Reconstruction



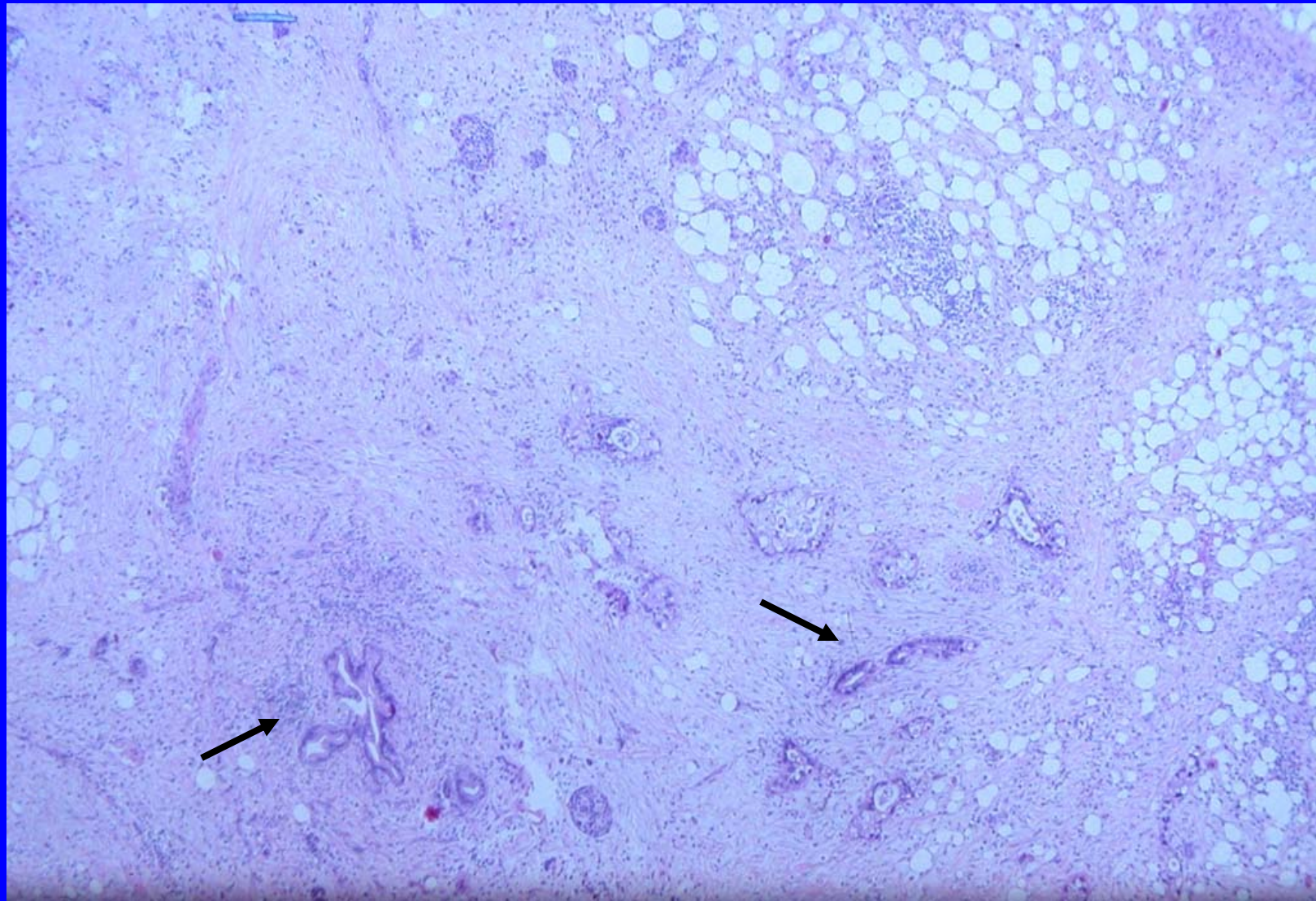
Survival

	Total/123	Rate
5 year Survivors	18	14.6%
10 year Survivors	5	4.06%

Pancreatic Cancer Survival



Pancreatic Cancer - Histology



Somatic Mutations in Pancreatic Cancer

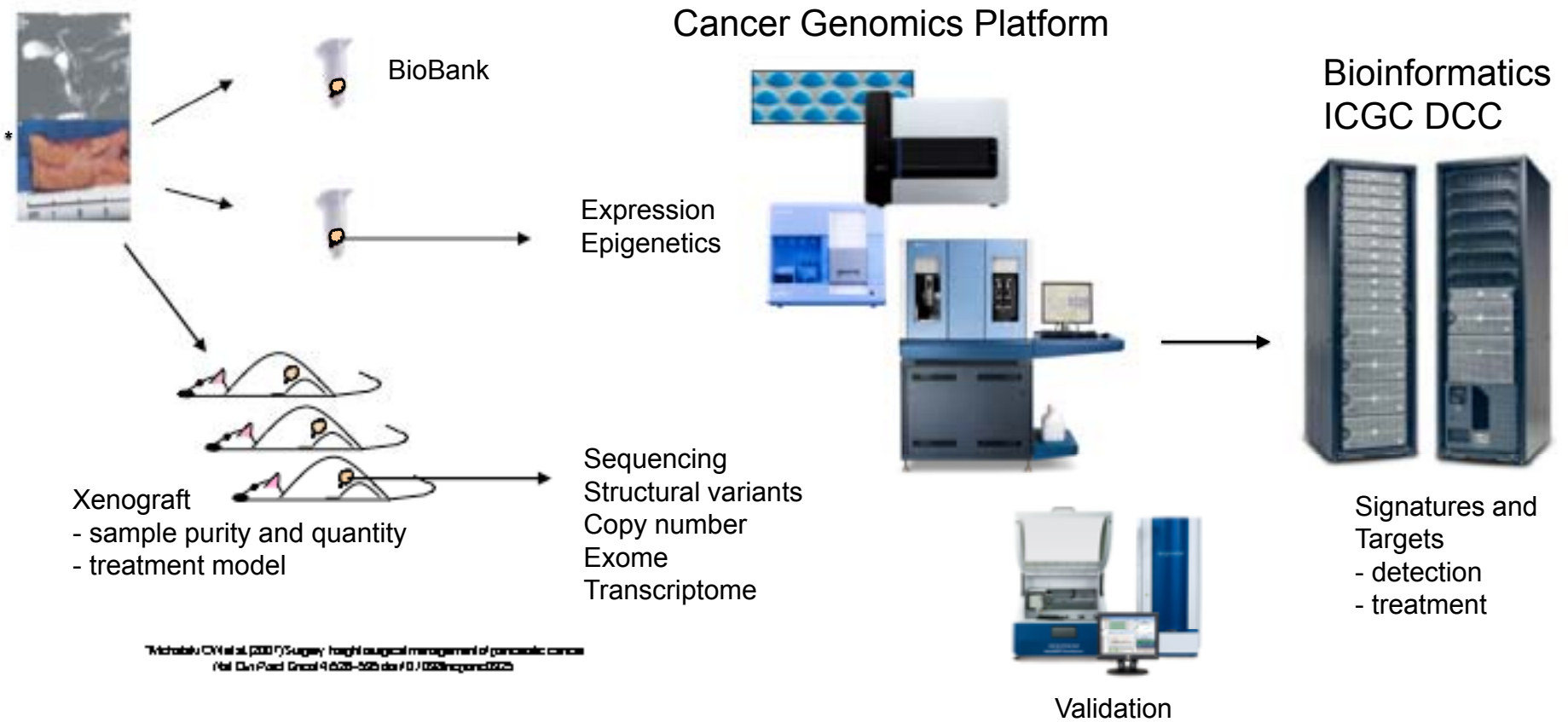
Gene or Region	Frequency of Alteration (% of tumors)
<i>K-ras</i>	>90
<i>p16</i>	>95
<i>p53</i>	50 - 75
<i>DPC4</i>	55
Chromosome 19q/AKT2	10 - 20
Chromosome 6q/MYB	10
Chromosome 20q/AIB1	10
<i>BRCA2</i>	7 - 10
<i>LKB1/STK11</i>	4
<i>MKK4</i>	4
TGF- β R-I or R-II	<5
<i>RB1</i>	<5

Pancreas Cancer Xenograft





OICR International Cancer Genome Consortium Pancreatic Cancer Genome Project



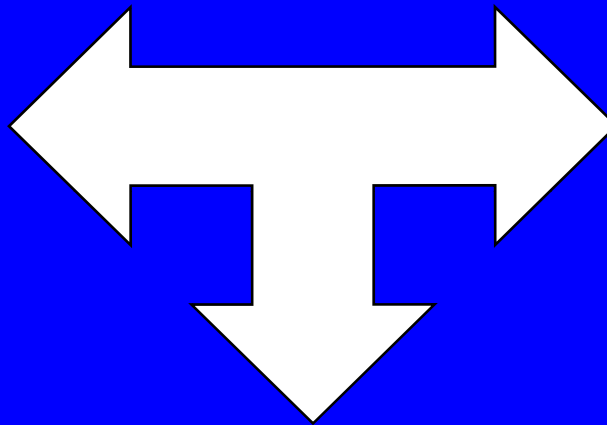
Pancreatic cancer: Causes

Environmental factors

- **Smoking**
- Alcohol
- Coffee
- Diet
- Chemicals

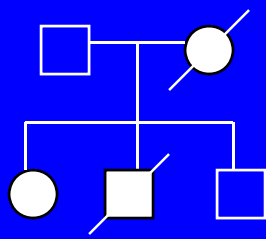
Host factors

- Past medical history
- Pancreatitis

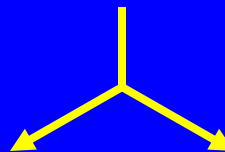


Genetic Predisposition

Familial
Aggregation
of cases



Familial cancer
syndromes



Family History

~5-10% of pancreatic cancer is
'hereditary'

- known hereditary cancer syndromes
- familial pancreatic cancer (FPC)

Known Hereditary Syndromes

Syndrome	Gene	Estimated risk of pancreas cancer
Hereditary Breast/Ovarian Cancer	BRCA2 BRCA1	5-7% 2-3%
Familial Atypical Multiple Mole Melanoma (FAMMM)	CDKN2A p16-Leiden mutation	5-8% ~15-20%
Peutz-Jeghers Syndrome (PJS)	STK11	8-36%
Hereditary Pancreatitis	PRSS1/SPINK1	40%

Pancreas Cancer Genetics Program

Familial GI Cancer Registry - MSH 1995-2000

NCIC - Moore/Narod/Gallinger

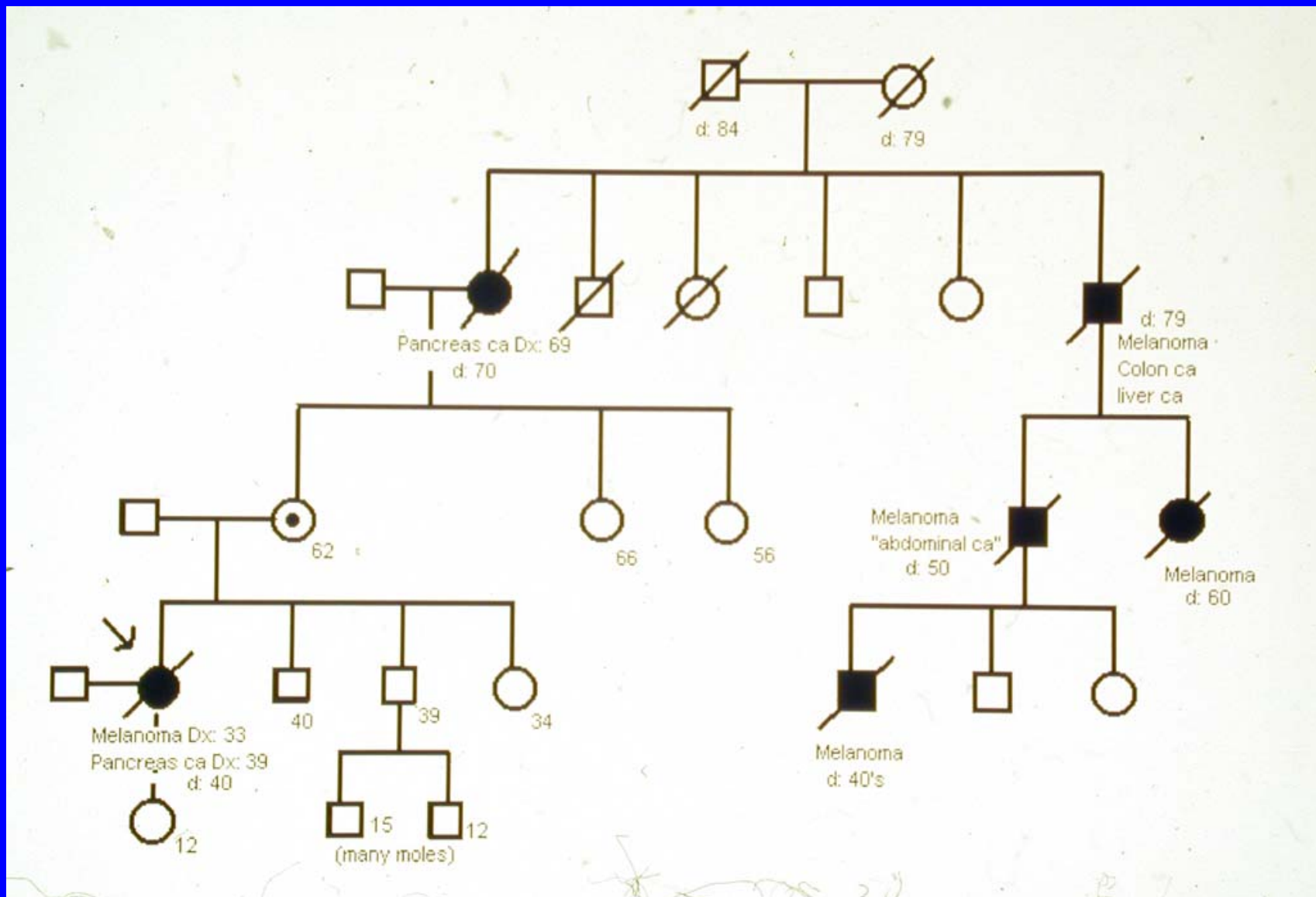
OCRN - Ontario Pancreas Cancer Study (OPCS)

Moore/Urbach/Cotterchio/Gallinger - 2000-2003

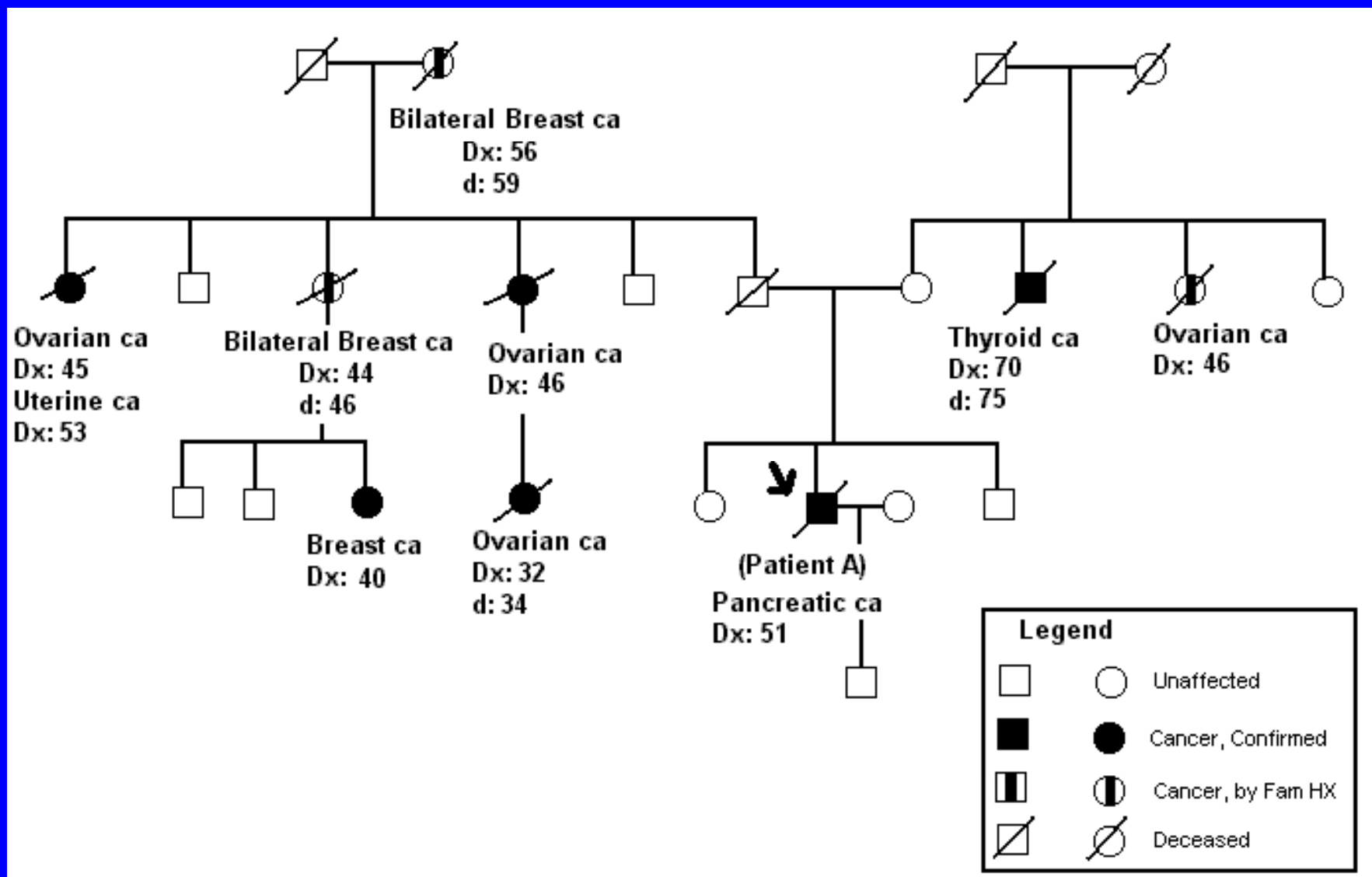
PACGENE - NIH - Gallinger - 2002-2008

Expansion of OPCS - clinic-based recruitment - Liu
(PMH) - Zane Cohen Digestive Disease Centre - Hung
(MSH)

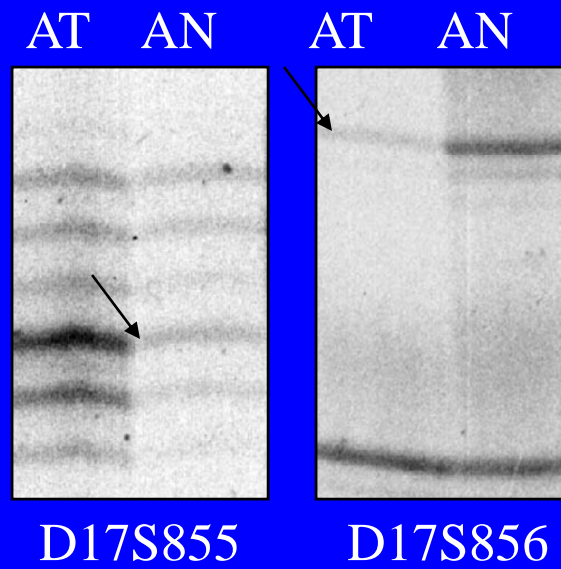
Melanoma + Pancreas Cancer



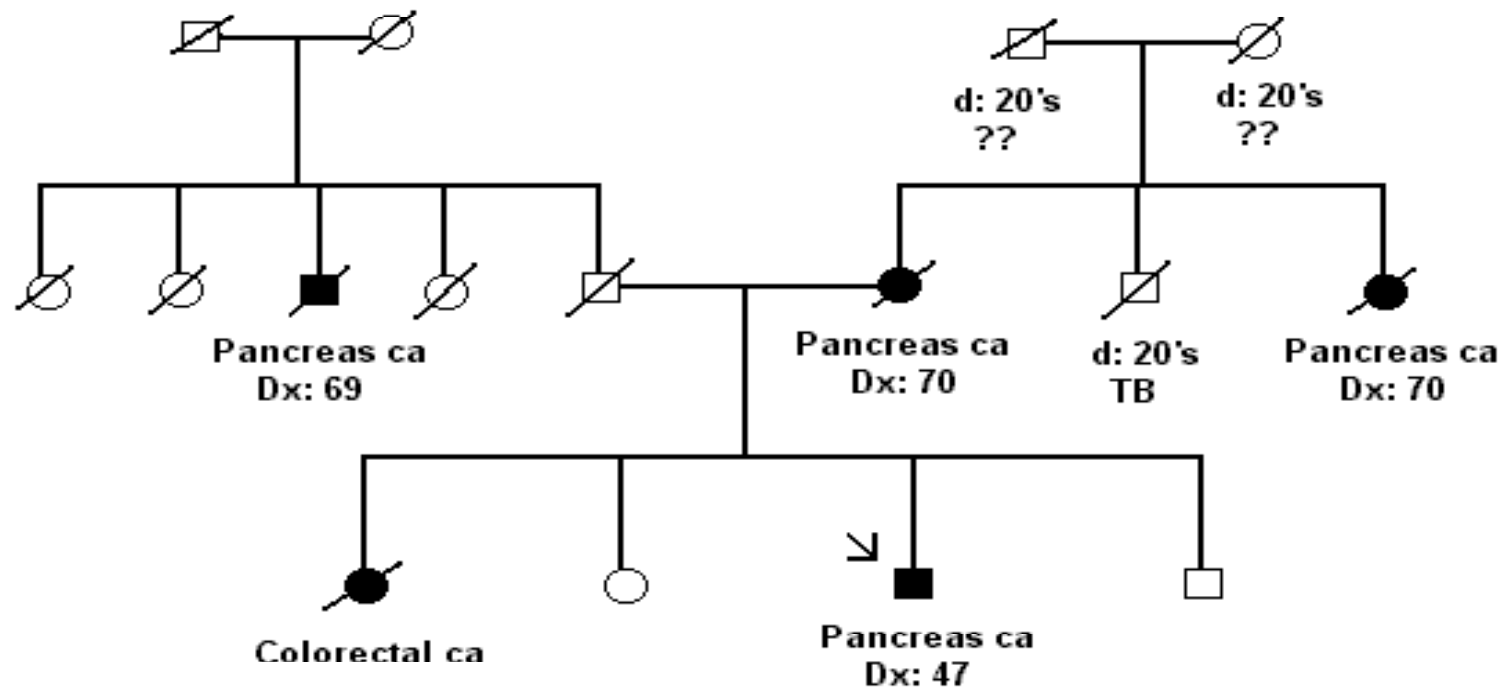
Breast/Ovarian Cancer + Pancreas Cancer



BRCA2 LOH



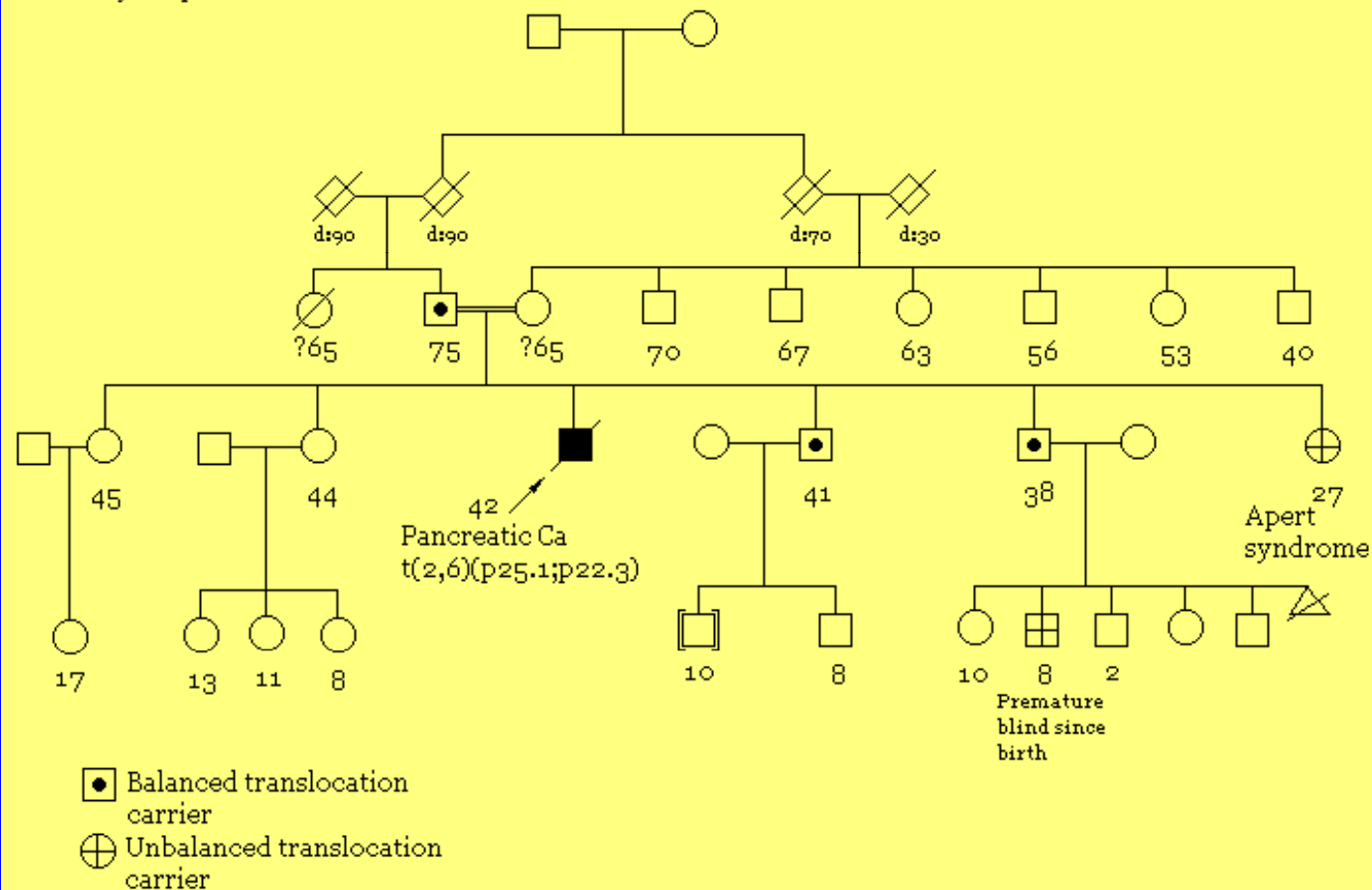
Familial Pancreatic Cancer



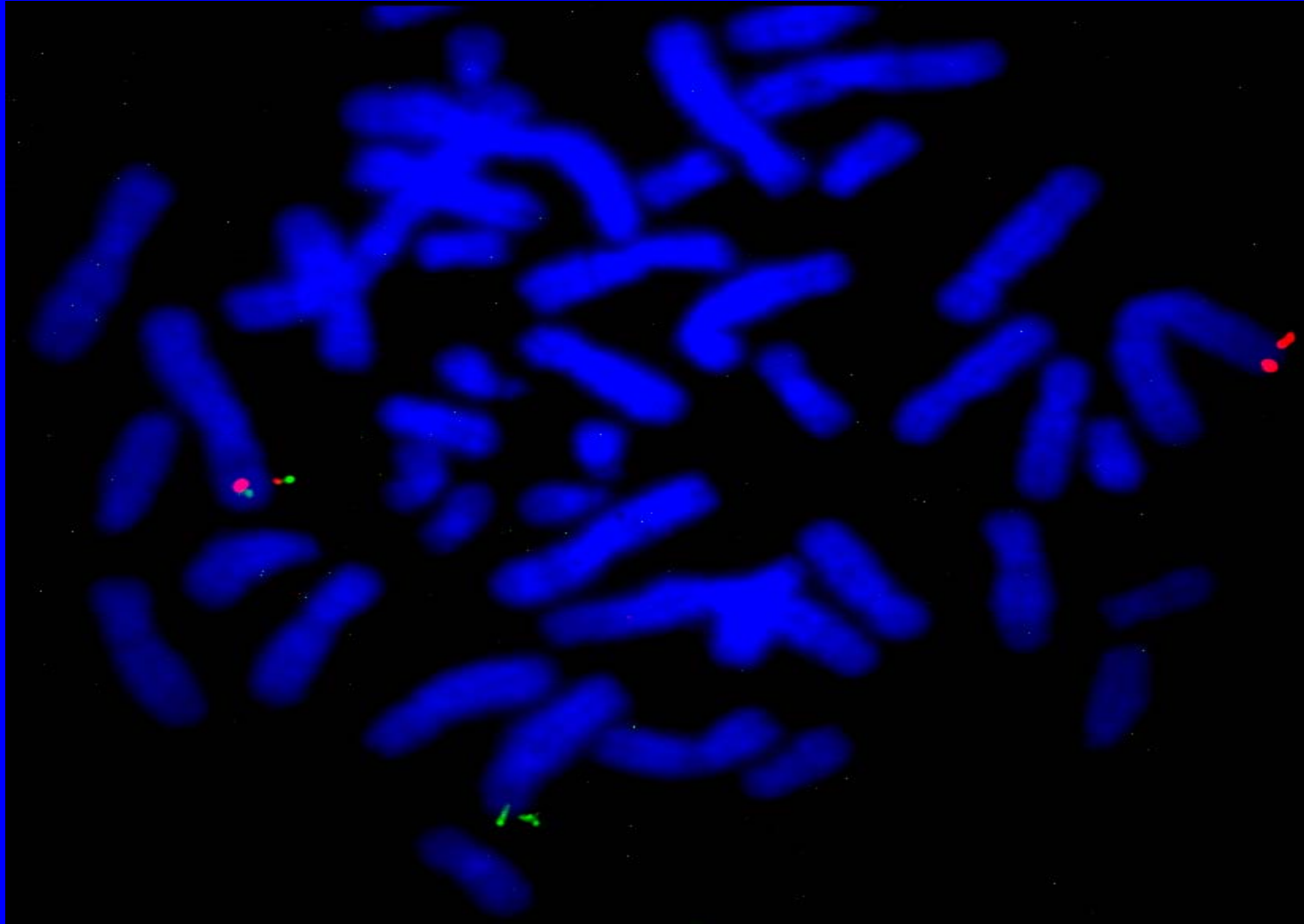


Novel Germline Translocation in a Young Pancreatic Cancer Patient

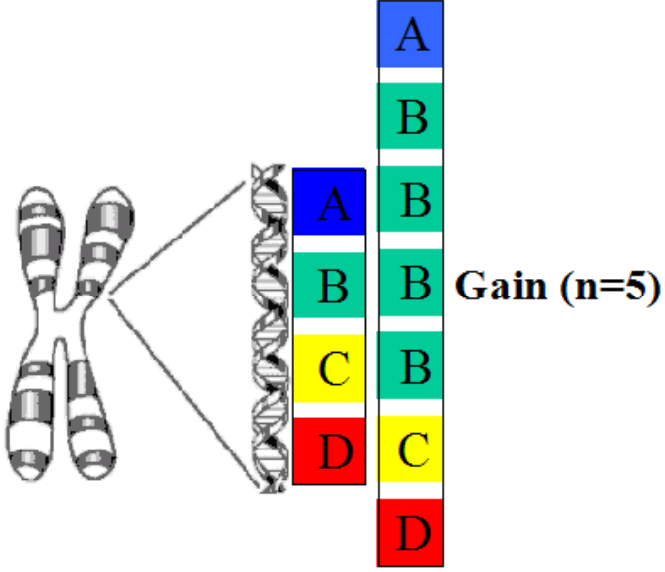
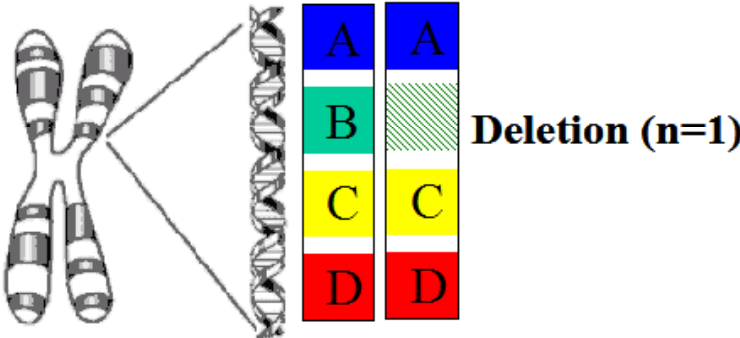
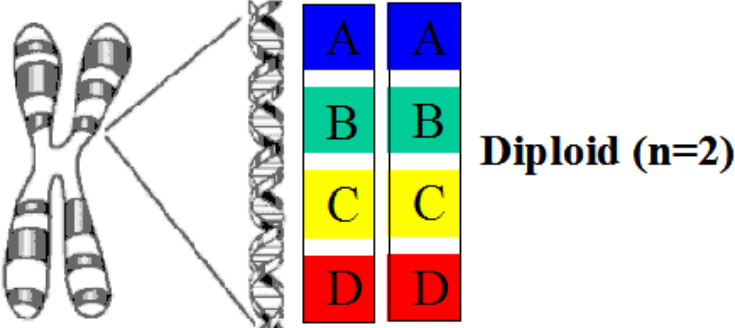
Ethnicity: Sephardic Jewish



Localization of Translocation with Fluorescent *in Situ* Hybridization (FISH)



Germ-line DNA Copy Number Variation(CNV)



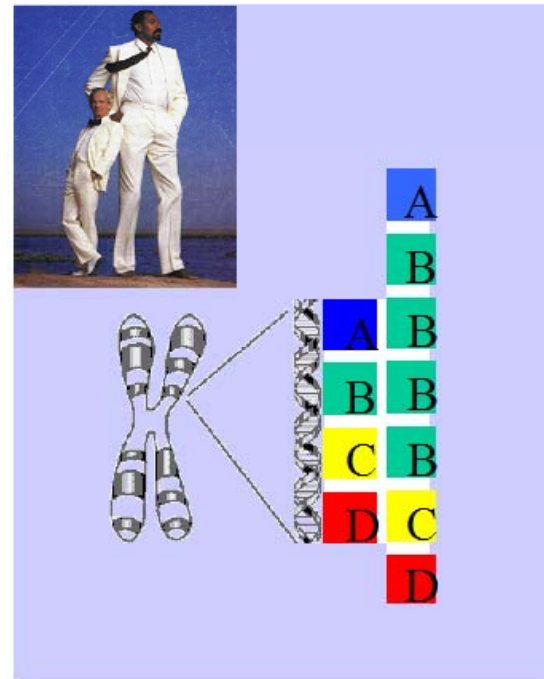
Role of Genetic Variation in Disease

SNPs (1bp)



10 Million @ >1% freq

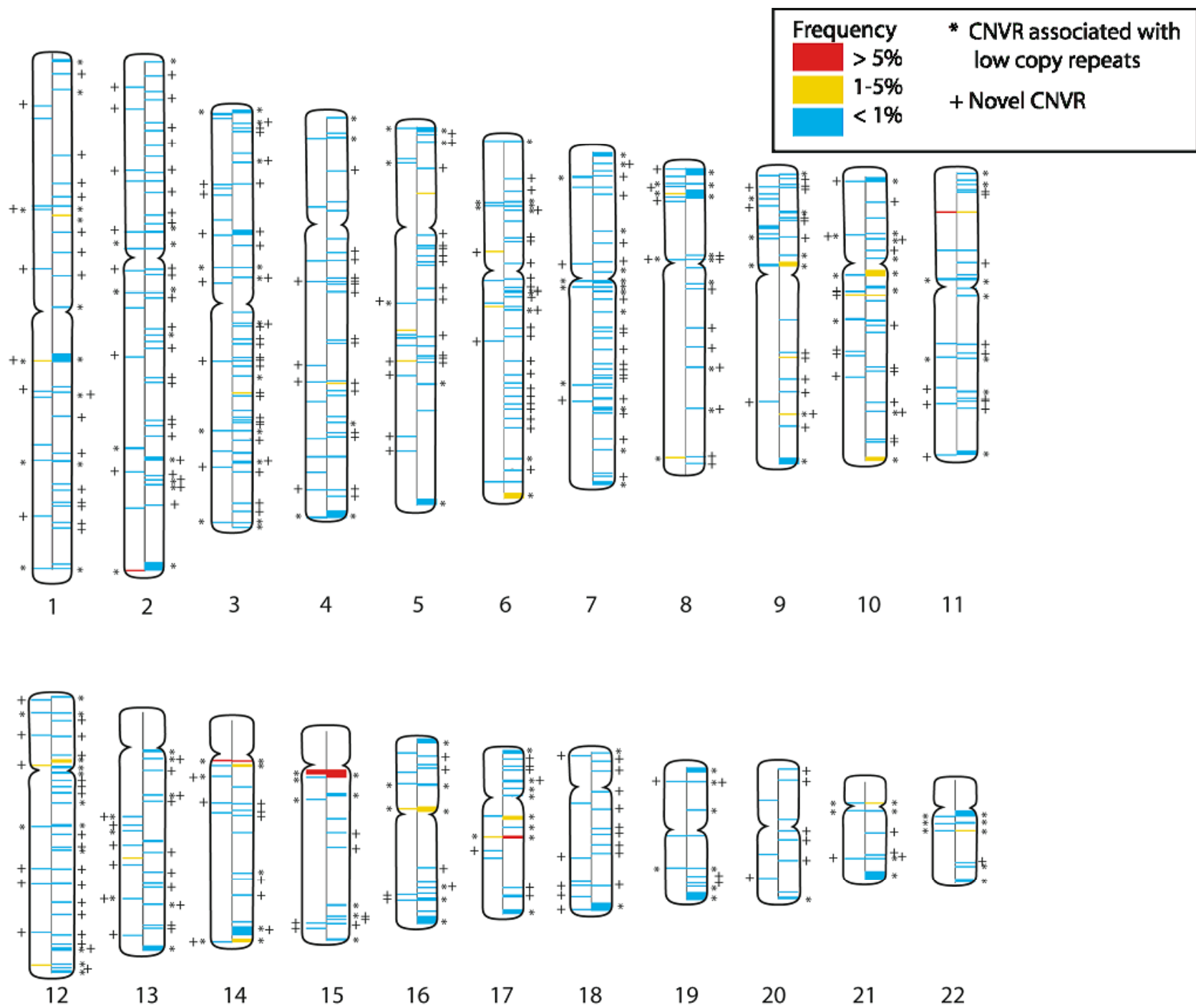
CNVs (>1kb)



? thousands @ ? % freq

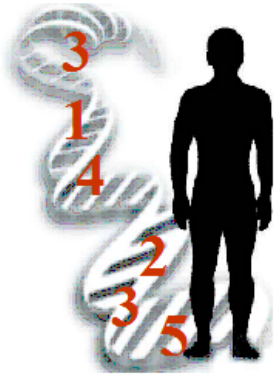
Vs.





123 PACGENE subjects

**Mayo, Ontario, MDACC,
Nebraska, Karmanos**



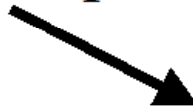
**All 4 chips analyzed
separately**



**Filter criteria to reduce noise
in copy number data**

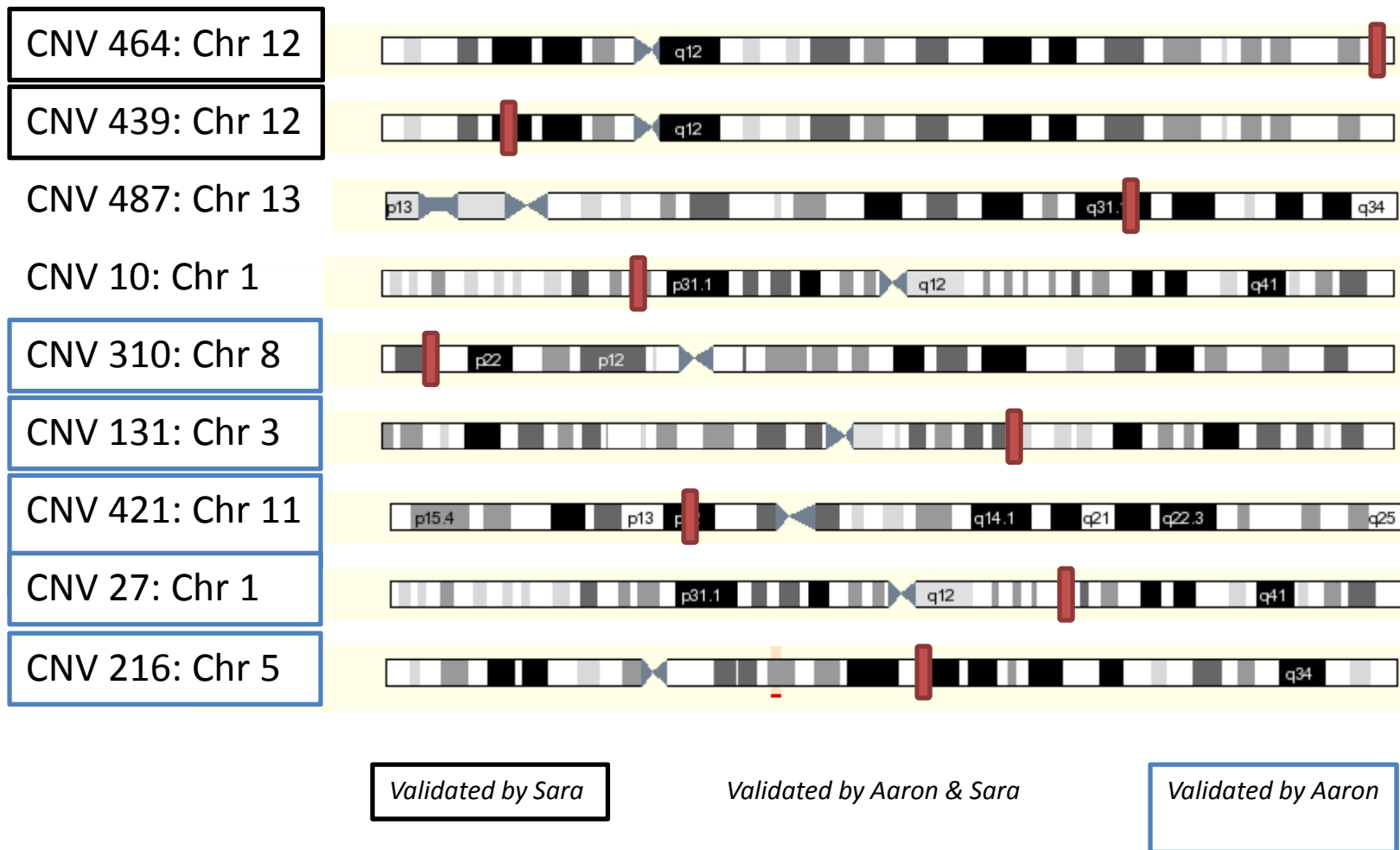


**Merged filtered data from all 4
chips across all 1190 samples**

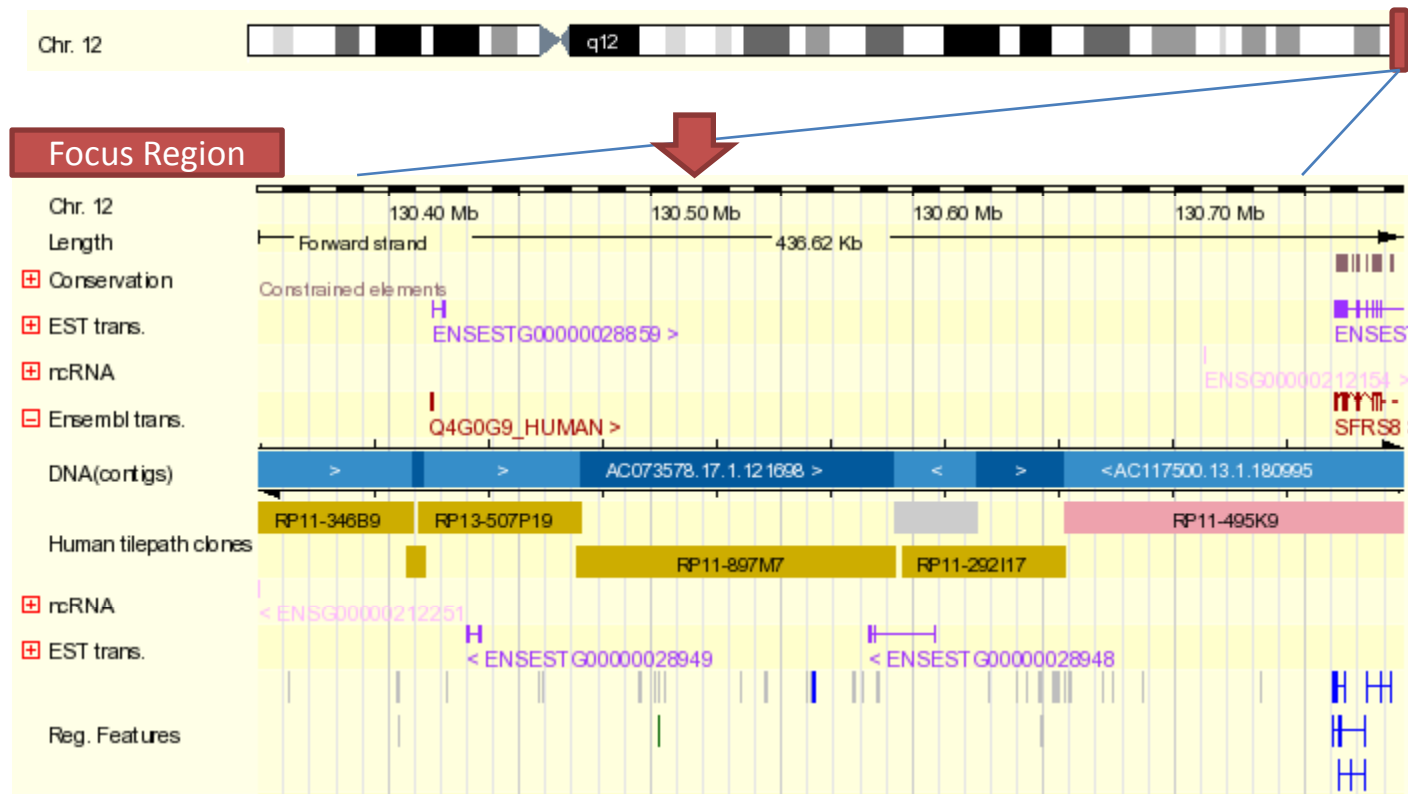


Identified Copy Number Variable Regions
Breakpoint = chromosomal position where intermarker
distance >1Mb

CNVs Validated by qPCR



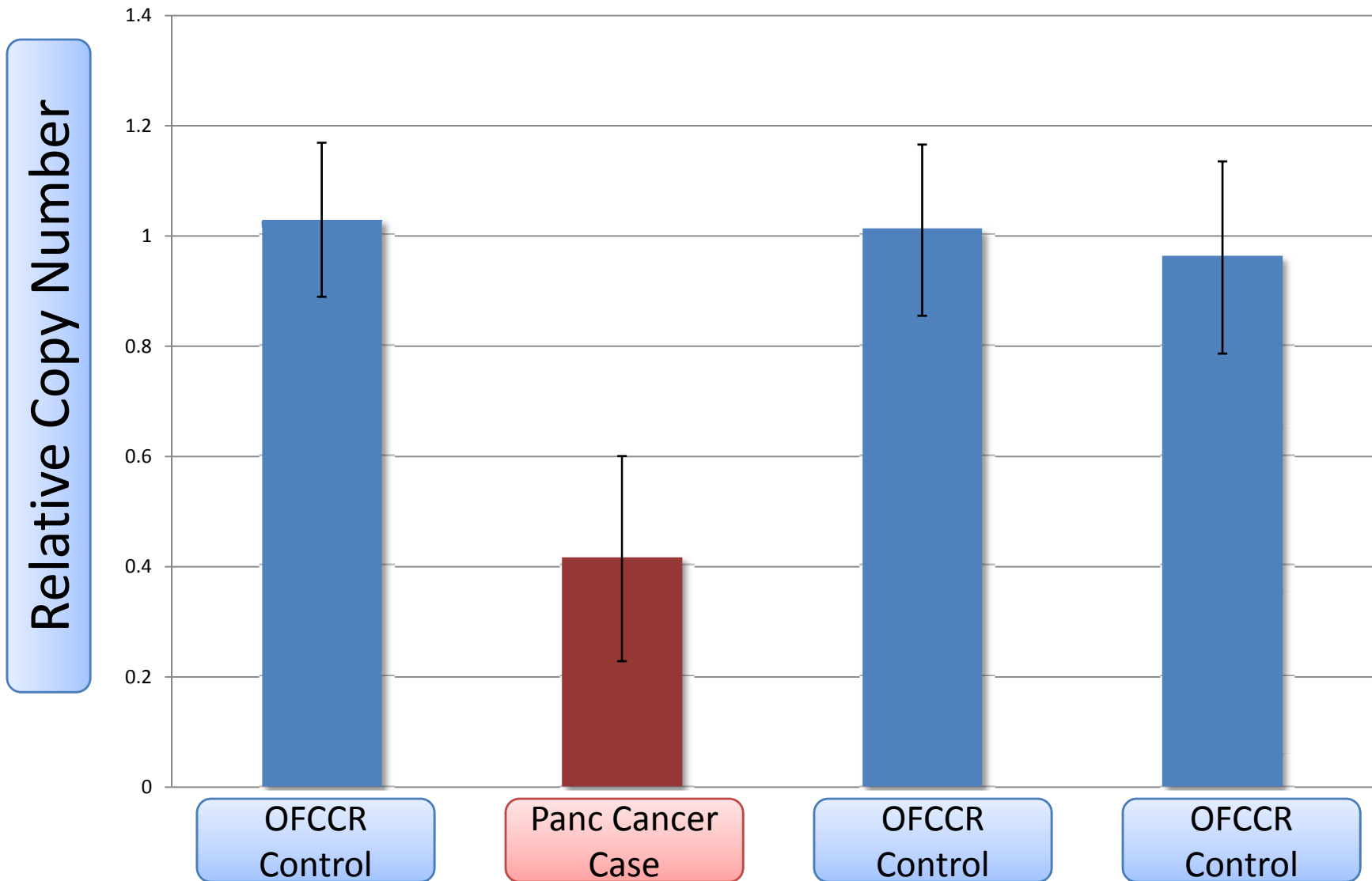
CNV 464



Chr	Start	End	Size	NSP & STY SNPs	Algorithm	Chip
12	130350201	130786816	436616	91	dechip/ cnag/ cnat/	Nsp/sty

Genes	mRNA	EST	miRNA	Nearest Gene	Cont	Cases
n	y	y	n	SFRS8	n	1

CNV 464



Survival Analysis

		Mean Survival (months)	Univariate Analysis	Multivariate Analysis
Jaundice	Yes	29.9	p<0.05	
	No	43.2		
Tumour size			p<0.05	
Lymph Node	Pos	22.8	p<0.005	
	Neg	43.4		
Stage	1	67.0	p<0.01	p<0.01
	2	31.1		
	3	22.8		
	4	25.6		
Grade	Well	61.2	p<0.003	p<0.003
	Mod	28.5		
	Poor	23.4		

Pancreas Cancer Screening Program

MSH/UHN

- Yearly transabdominal US and MRI
- Blood sampling for future biomarkers
- Psychosocial questionnaires
- Epidemiological questionnaires
- Genetic counselling

Eligibility Criteria

- 1) FPC (≥ 2 relatives in the same lineage with panc ca)
- 2) BRCA2 or p16 carriers (fam hx of panc ca not required)
- 3) BRCA1 carriers (fam hx of panc ca required)
- 4) relatives of pts with multiple cancers (one is panc ca)
- 5) PJS
- 6) hereditary pancreatitis

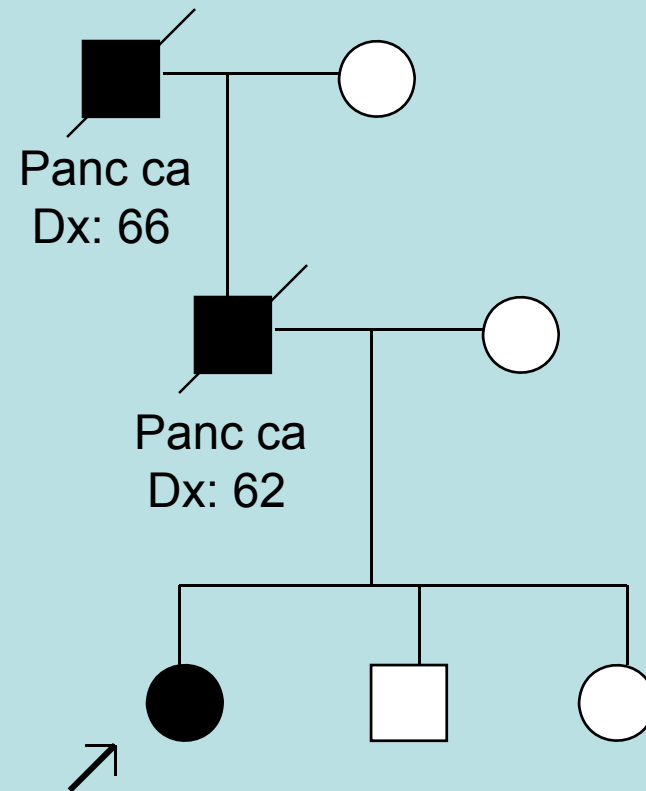
age 50, or 10 years younger than the youngest dx of panc ca in the family for criteria 1-4, age 25 for PJS, and age 35 for individuals with HP

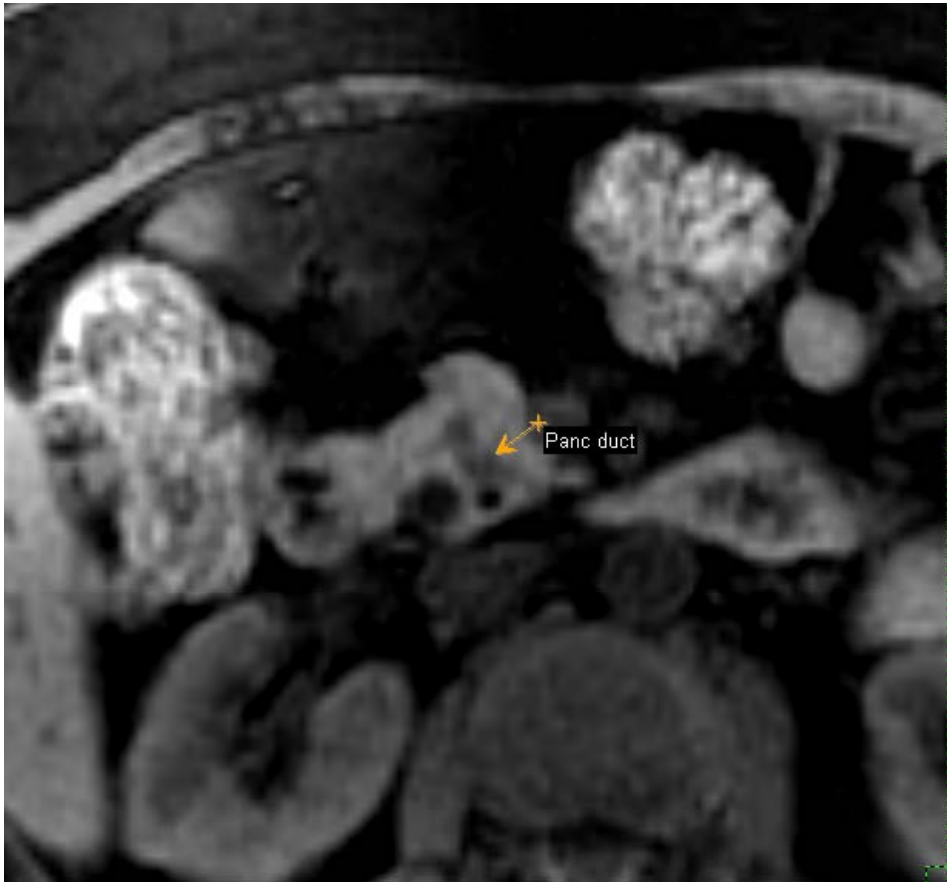
Study Participants

- 241 recruited since 2003
- 67.2% female
- average age 53 (range 22-87)
- 1/3 of participants travel > 100km to participate at their own expense.

Case 1: Pancreas Adenocarcinoma

- 57yo female with FPC
- 1.5cm mass
- total pancreatectomy based on local invasion and ductal atypia.
- Invasive adenocarcinoma, with multifocal PanINs 1/3 and one positive node.
- alive 14 months post-op





Case 4: PanIN

- 54yo female with FPC
- 1.5 x 0.7cm multilobulated cystic lesion body/tail, 0.6cm cyst in the panc tail, and a third 0.3cm cystic lesion in panc tail.
- Distal pancreatectomy.
- PanIN1-2

