ESMO PRECEPTORSHIP ON PANCREATIC ADENOCARCINOMA

Epidemiology, molecular characterisation and hereditary forms of pancreatic cancer

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06/11/2019

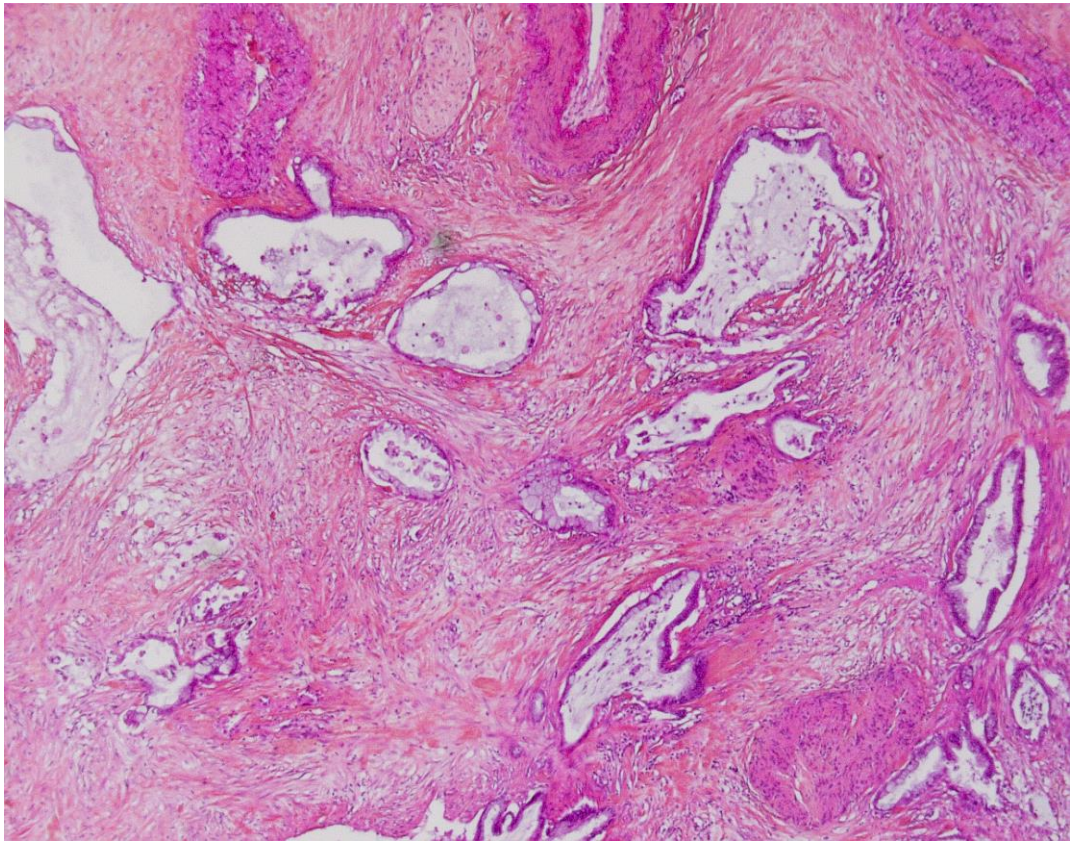
Disclosures

Research grant: Halozyme

Travel grant: Novartis, Pfizer

Pancreatic cancer?

Adenocarcinoma (90%)

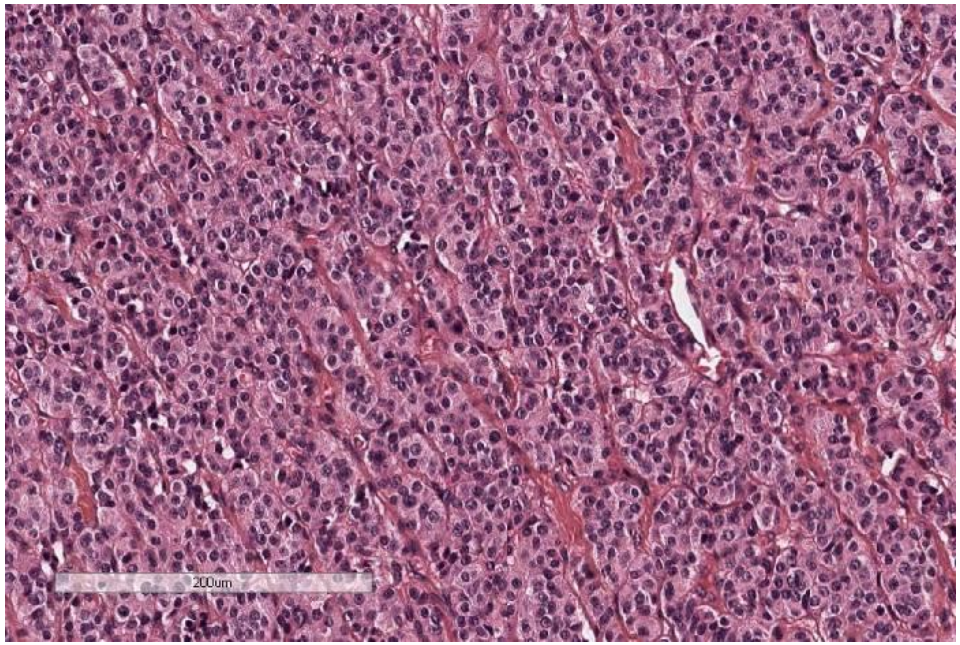


Pancreatic cancer?

Adenocarcinoma (90%)

Neuroendocrine lesions

Rare lesions: Acinar cell carcinomas….

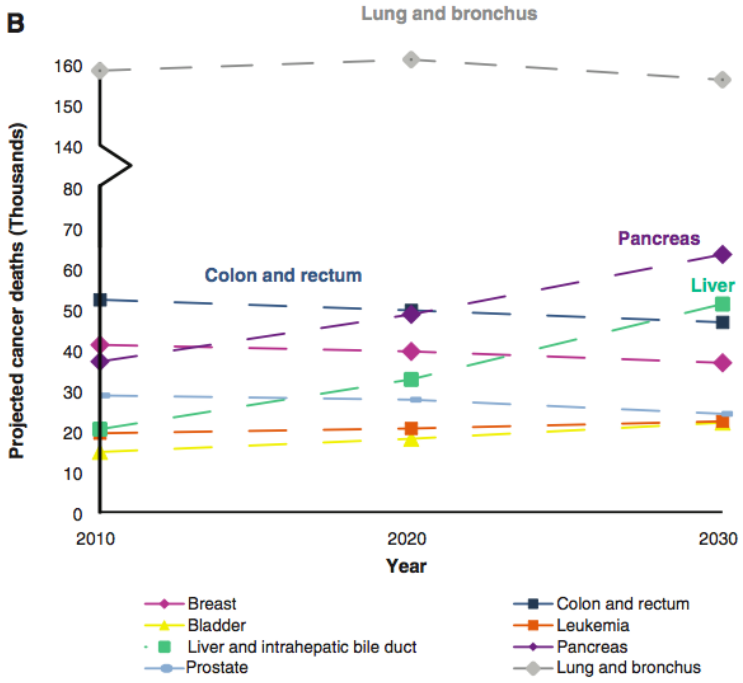


Completely different morphology, biology, treatment (sometimes)….

Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States

Lola Rahib[1], Benjamin D. Smith[2], Rhonda Aizenberg[1], Allison B. Rosenzweig[1], Julie M. Fleshman[1], and Lynn M. Matrisian[1]

Cancer Res - 2014
74(11); 2913–21



We're not out of the wood… Just getting in!

Cancer sites	Men AAPC[a]	Men # of Cases[b]	Women AAPC[a]	Women # of Cases[b]	All # of Cases[b]
Pancreas					
2010	1.3	22,000	1.4	22,000	43,000
2020		31,000		31,000	62,000
2030		43,000		44,000	88,000

V. Rebours

European cancer mortality predictions for the year 2014

M. Malvezzi[1,2], P. Bertuccio[1], F. Levi[3], C. La Vecchia[2*] & E. Negri[1]

[1]Department of Epidemiology, IRCCS-Istituto di Ricerche Farmacologiche 'Mario Negri', Milan; [2]Department of Clinical Sciences and Community Health, Universitá Degli Studi di Milano, Milan, Italy; [3]Cancer Epidemiology Unit, Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital, Lausanne, Switzerland

Annals of Oncology, 2014

More deaths from pancreatic cancer than breast cancer in the EU by 2017

J. Ferlay[a], C. Partensky[b] and F. Bray[a]

Acta Oncologica 2016

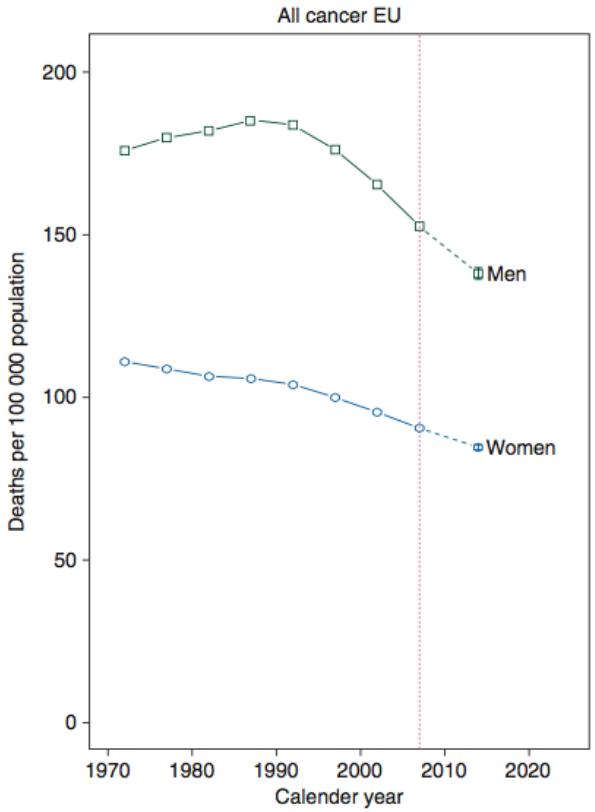


Figure 2. Age-standardized (world population) total cancer mortality trends in quinquennia from 1970–1974 to 2005–2009 and predicted rates for 2014, for men (squares) and women (circles) in the EU.

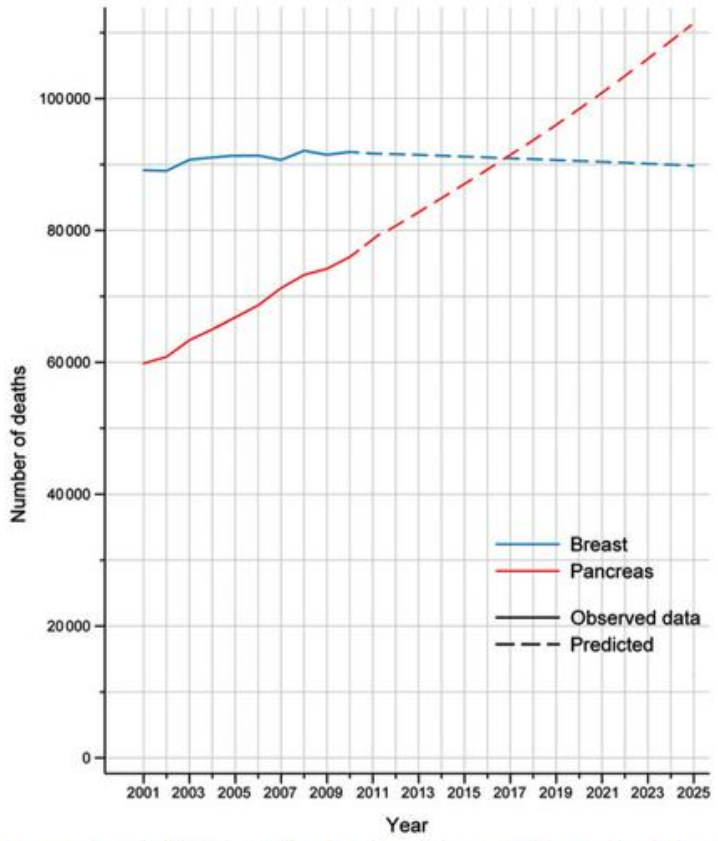
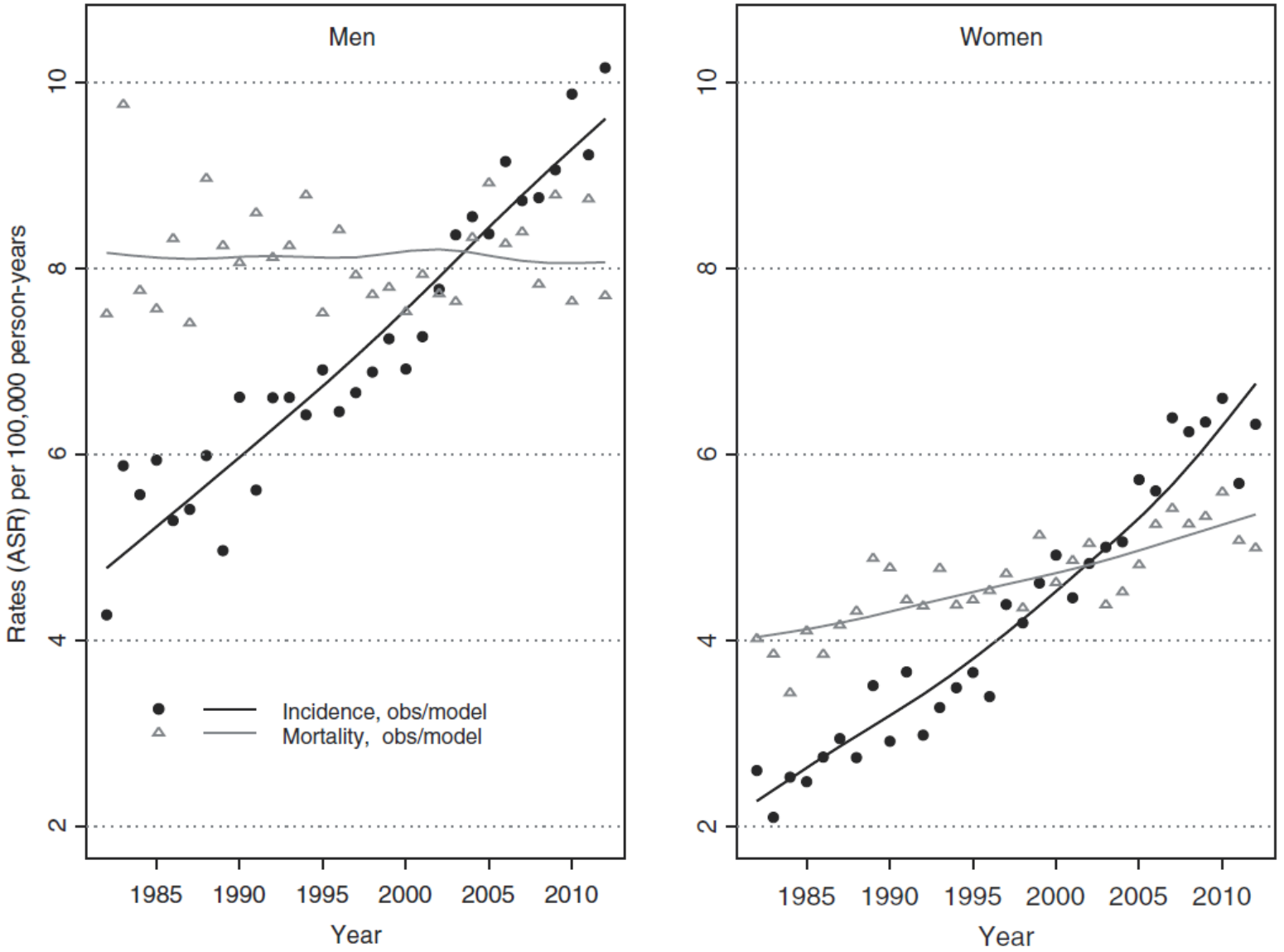


Figure 1. Recorded (2001–2010) and projected (up to 2025) number of breast and pancreatic cancer deaths (both males and females) in the EU.

V. Rebours

Incidence has been rising continuously in the last 30 years: France



V. Rebours

Bouvier. *et al. Int J Epidemiol* 2017

Incidence is higher in the western world

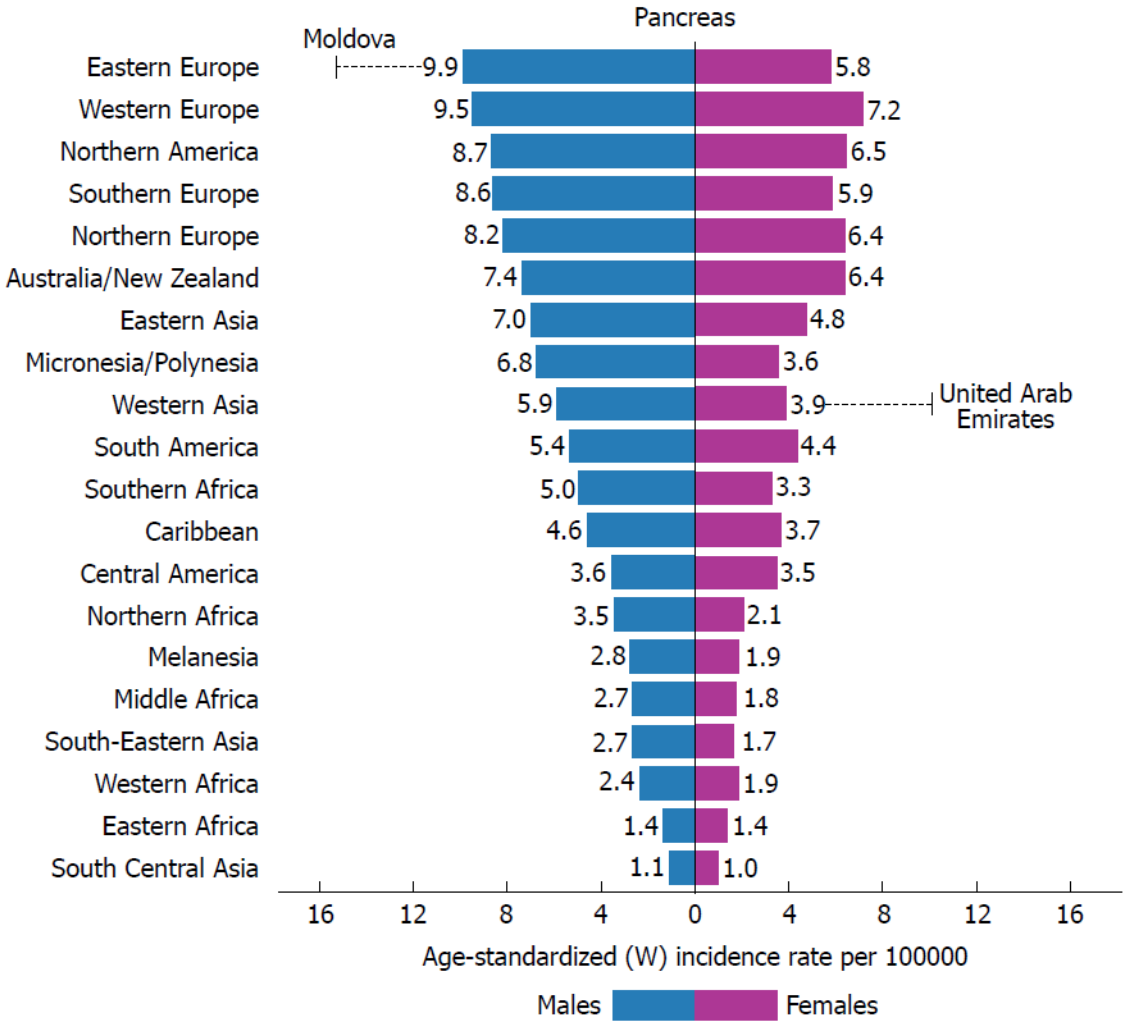
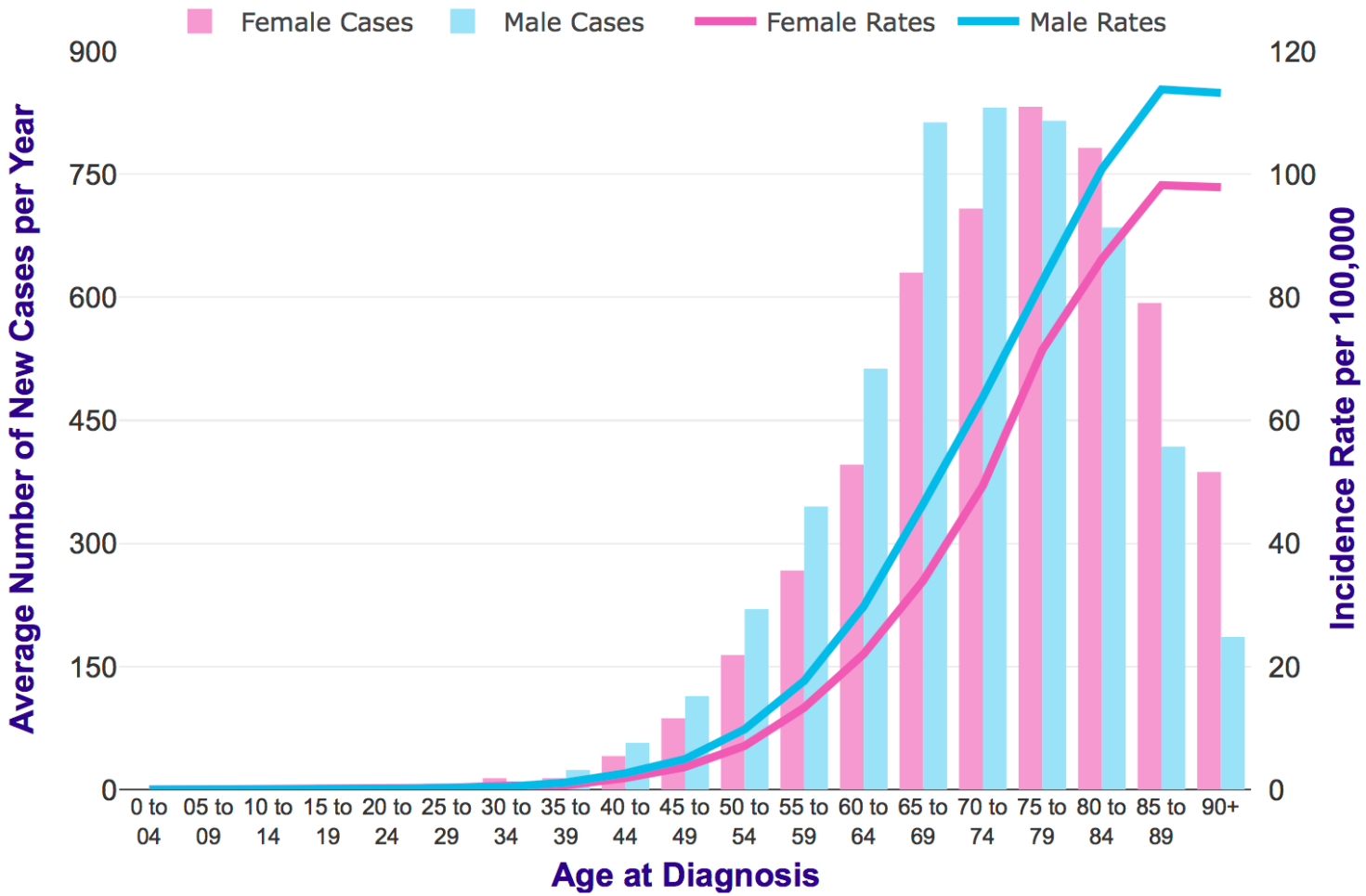


Figure 1 Diagram of incidence of pancreatic cancer in both sexes throughout the world Adapted from Globocan[1] 2018.

V. Rebours

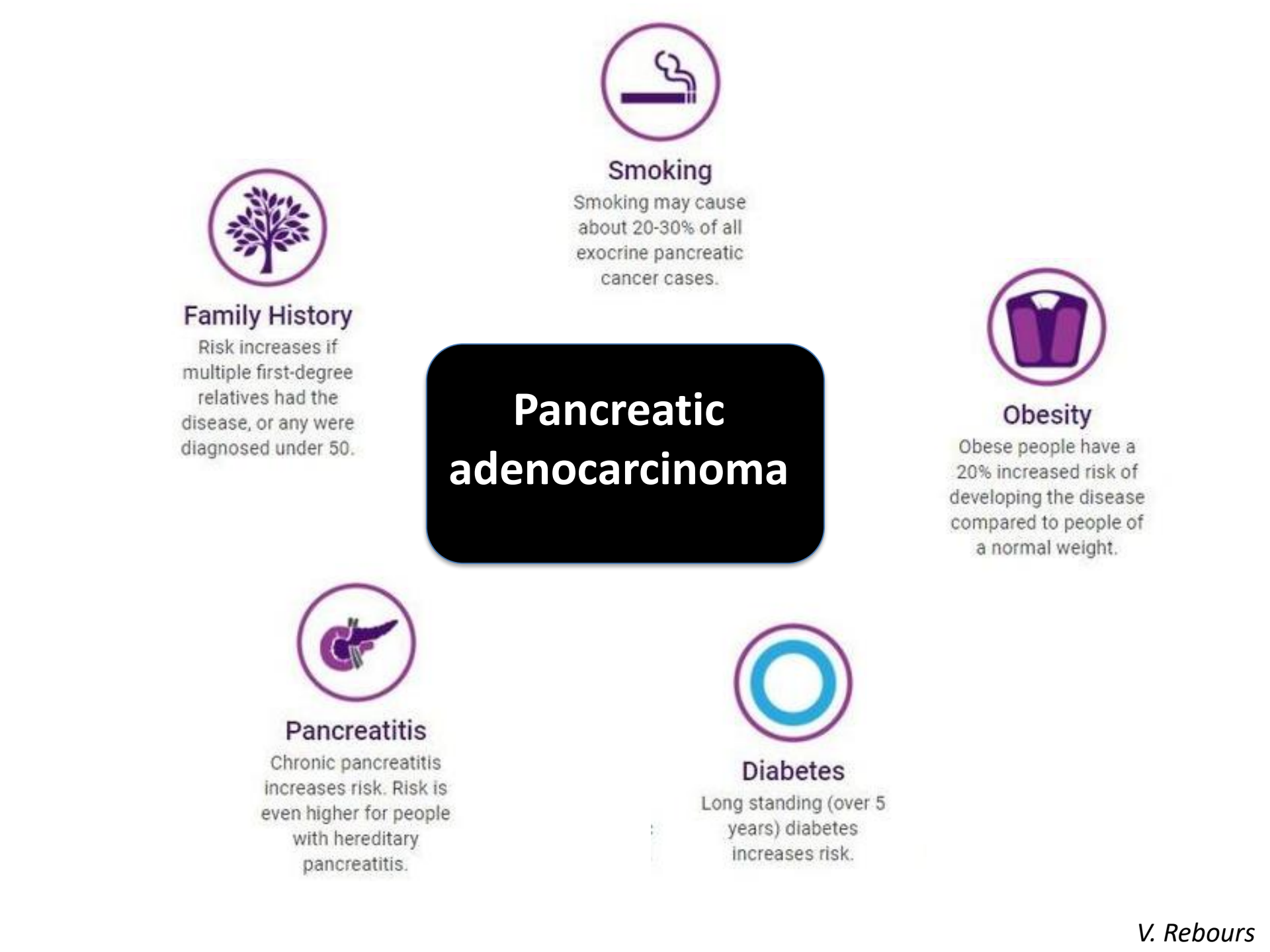
Mac Guigan *et al. World J Gastroenterol* 2018

Pancreatic Cancer (C25), Average Number of New Cases per Year and Age-Specific Incidence Rates per 100,000 Population, UK, 2014-2016



V. Rebours

From Cancer research uk


Smoking
Smoking may cause about 20-30% of all exocrine pancreatic cancer cases.
Family History
Risk increases if multiple first-degree relatives had the disease, or any were diagnosed under 50.
Pancreatic adenocarcinoma
Obesity
Obese people have a 20% increased risk of developing the disease compared to people of a normal weight.
Pancreatitis
Chronic pancreatitis increases risk. Risk is even higher for people with hereditary pancreatitis.
Diabetes
Long standing (over 5 years) diabetes increases risk.

V. Rebours

INFLAMMATION

Tobbacco
Chronic pancreatitis

Heavy alcohol intake
Helicobacter Pylori

DNA DAMMAGE

Tobbacco
Oxidative stress

DNA REPAIR

Mediterranean diet

CANCER

IMMUNITY

Allergies/Atopia
O blood type

INSULINO-RESISTANCE

Hyperglycemia
Diabetis
Overweigth/Obesity
Metabolic syndrome

GENETIC

Familial forms

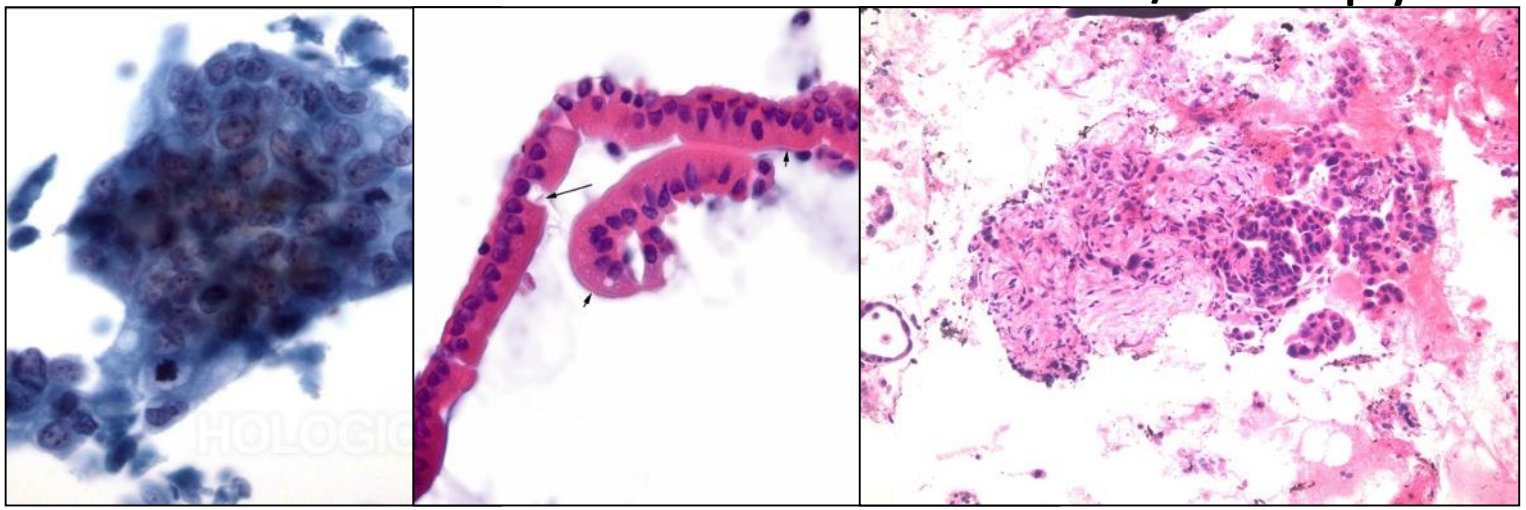
GLYCEMIA CONTROL

Metformine

V. Rebours

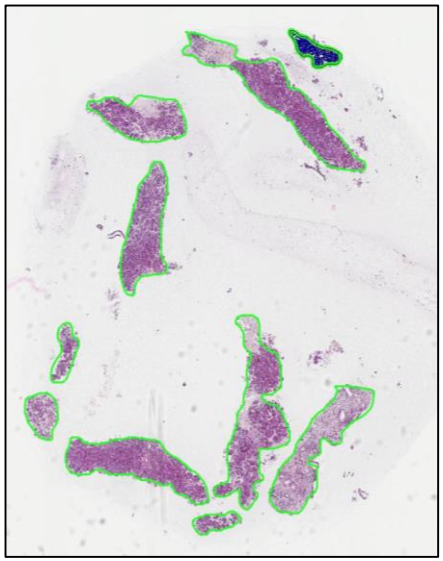
FOR GOOD DIAGNOSIS, GOOD RESEARCH STUDIES….

…WE NEED GOOD SAMPLES



Protein on Tum cells	OK	OK	OK
Mutation on Tum cell	+/- OK	++/- OK	OK
Exp (mi)ARN	+/- OK (amount/purity)	+/- OK (amount/purity)	+/- OK (amount/purity)
Protein in stroma	NO	NO	+/- OK

USE PROPER SAMPLING TECHNIQUES AND GOOD FNB NEEDLES

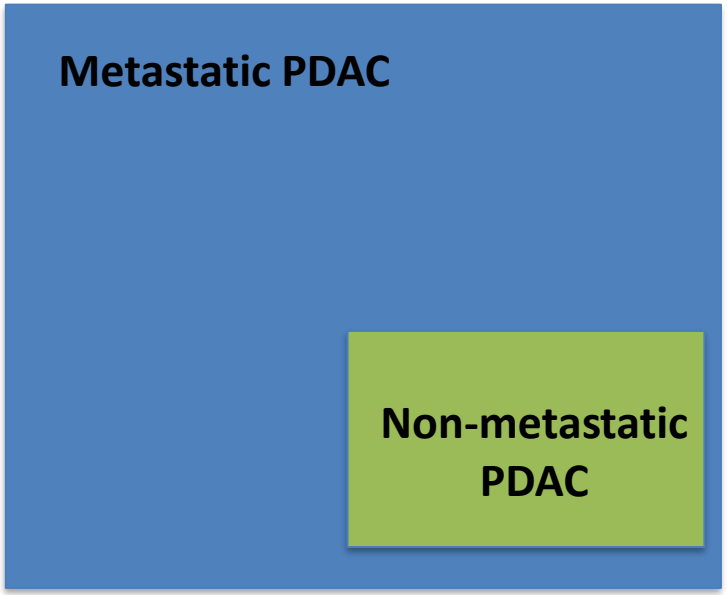


HISTOPAN (ClinicalTrials.gov ID: NCT03567863)
Multicenter randomized control trial
22-gauge Acquire® vs. 20-gauge Procore® (n=60)

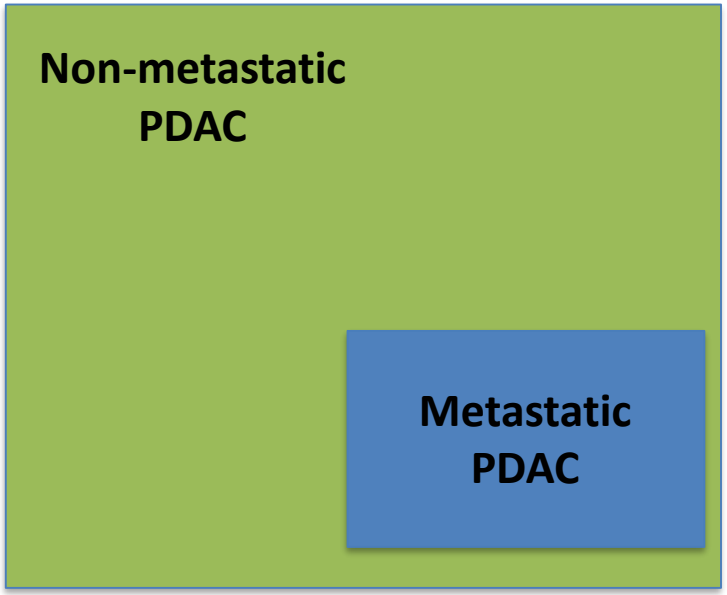
	Procore® 20G (n = 60)	Acquire® 22G (n = 60)	P value
Diagnosis obtained, n (%)	**40 (67%)**	**52 (87%)**	**<0.02**
Diagnosis of adenocarcinoma, n (%)	29/46 (63%)	38/46 (83%)	0.06
Diagnosis of neuroendocrine neoplasm, n (%)	9/11 (82%)	11/11 (100%)	0.5
Diagnosis of autoimmune pancreatitis, n (%)	1/2 (50%)	2/2 (100%)	1
Diagnosis of chronic pancreatitis, n (%)	1/1 (100%)	1/1 (100%)	1
Core biopsy obtained, n (%)	**49 (82%)**	**60 (100%)**	**<0.001**
Cumulative length of tissue core biopsies per needle pass, mean (SD), mm	5.42 (6.3)	11.36 (9.3)	<0.0001
Cumulative area of tissue core biopsies per needle pass, mean (SD), mm2	**1.77 (2.0)**	**3.48 (3.1)**	**<0.001**

Karsenti *et al. Submitted*

MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA

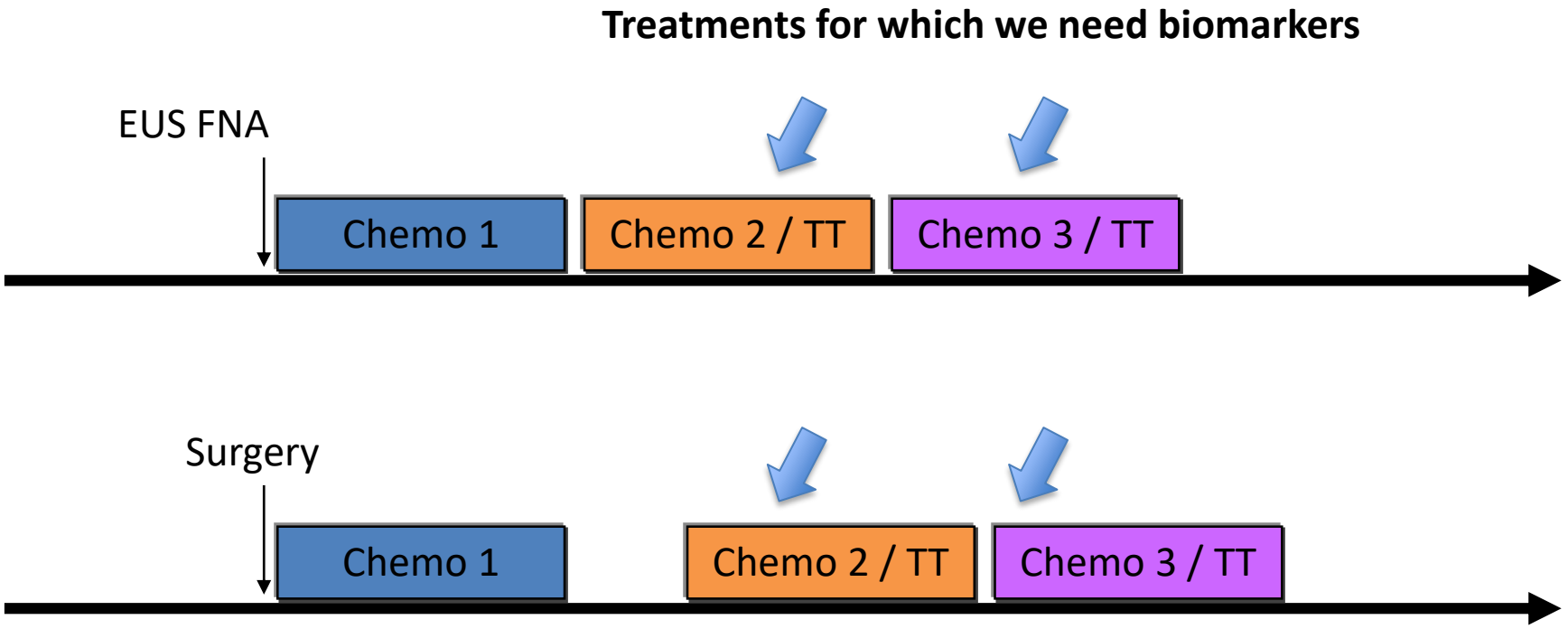


What we treat….



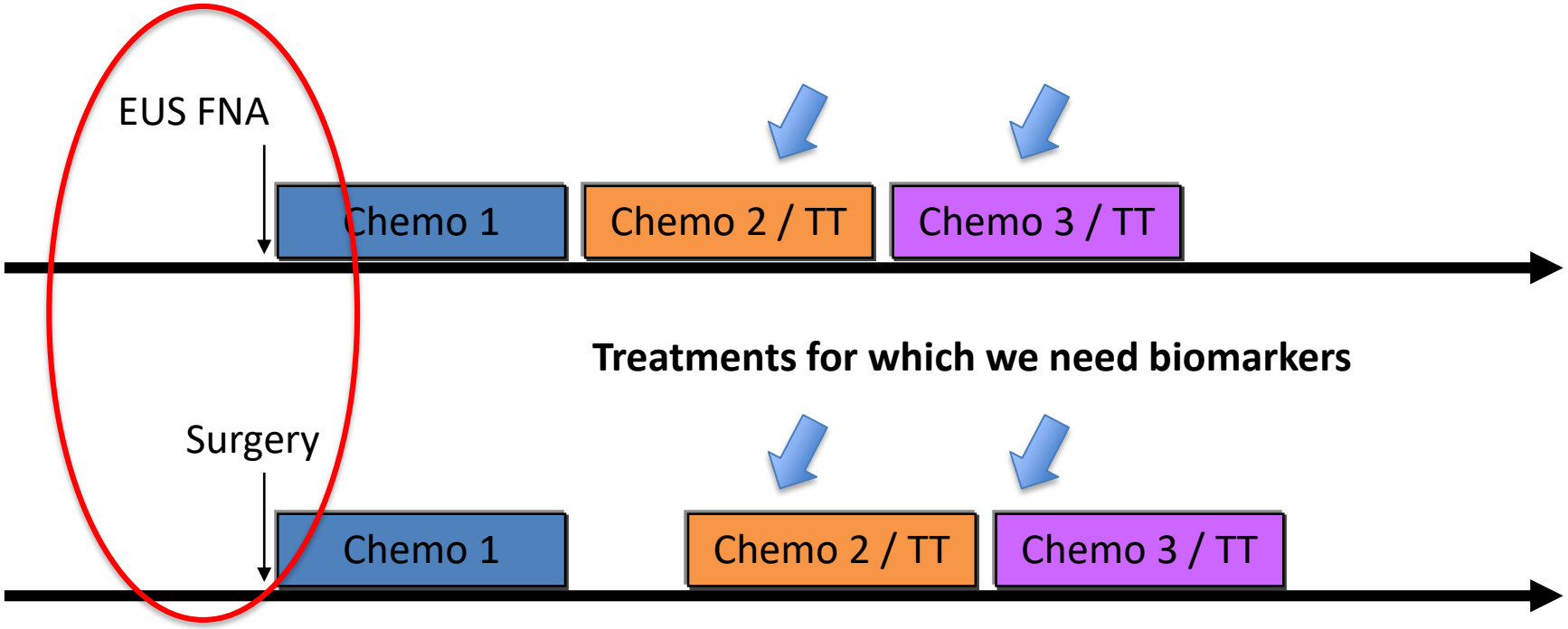
What we know (biology)….

MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA



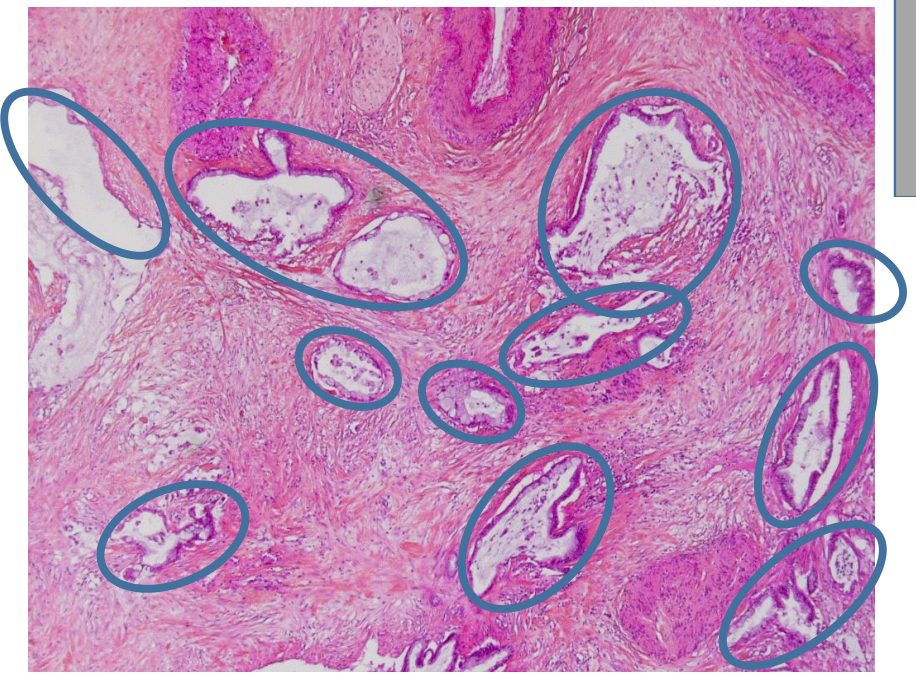
MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA

Samples on which we (try) to develop or test biomarkers…



This may impact clinical trials using biomarker-based patient stratification+++

MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA



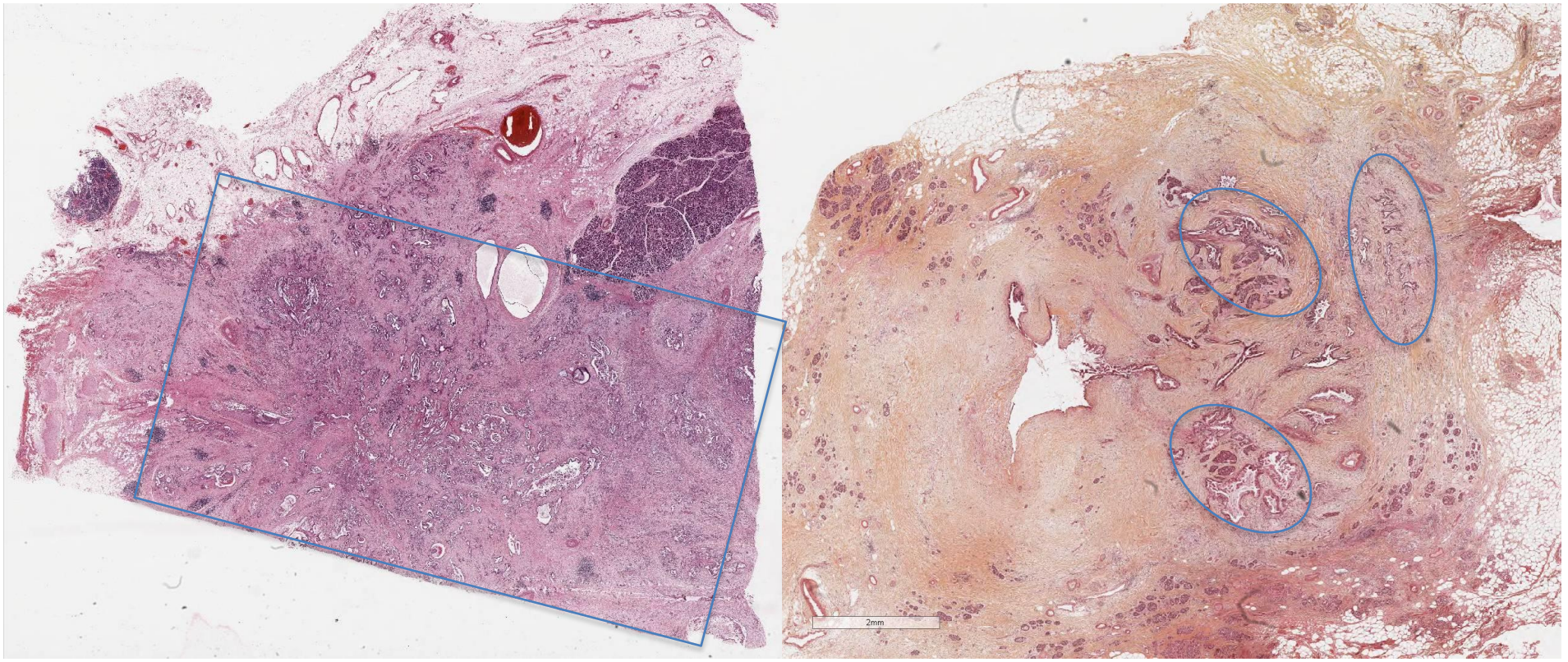
TUMOR

Tumor cells | Stroma

ECM | Vessels | Immune cells | CAF

MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA

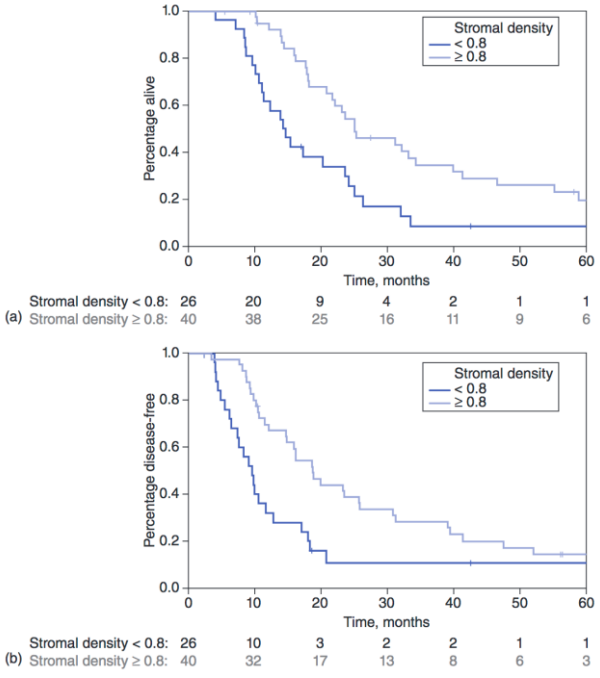
PDAC IS A HIGLY HETEROGENEOUS TUMOR, PROBABLY WITH A HIGHLY PLASTIC BIOLOGY



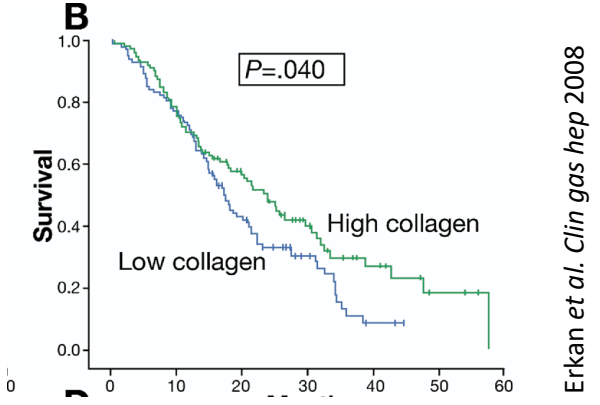
Heterogeneity of the tumor cell – stroma ratio

MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA

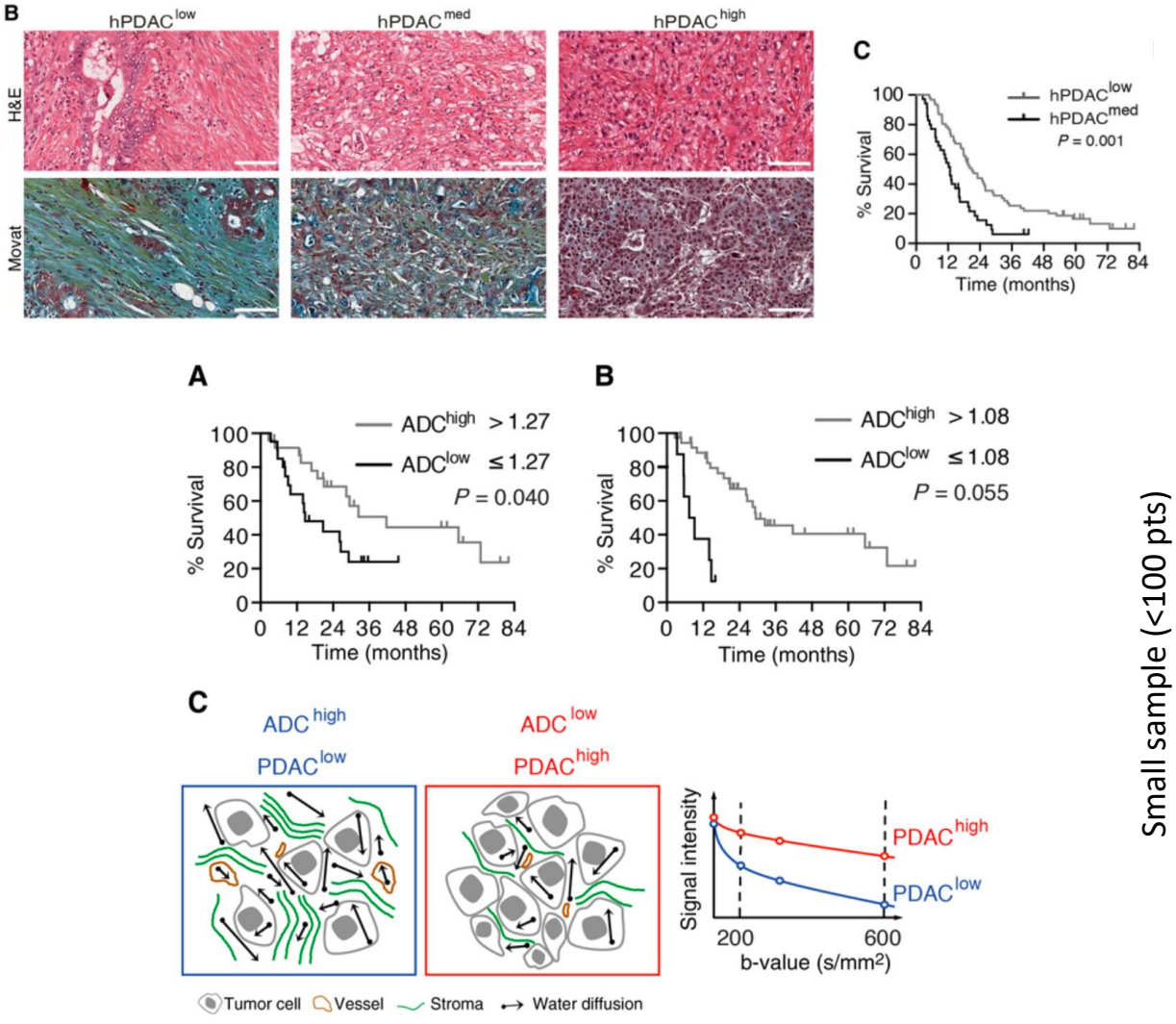
Stroma abundance– pronostic role?



Bever *et al. HPB* 2015, 292



Erkan *et al. Clin gas hep* 2008



Heid *et al. Clin can res* 2017, 1461

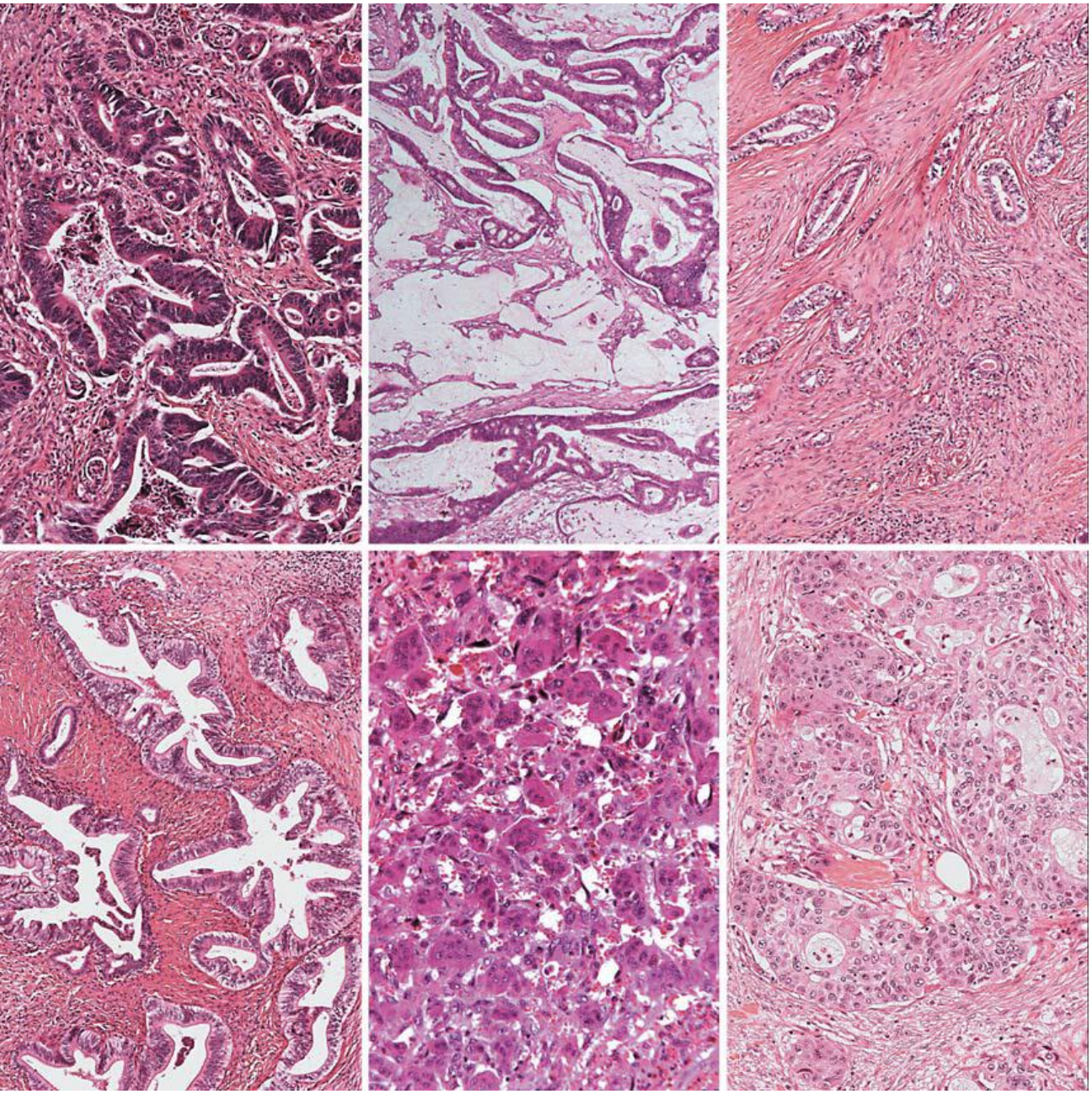
Small sample (<100 pts)

MORPHOLOGICAL HETEROGENETITY

intestinal

colloïd

ductal



micropapillary

Undifferentiated w/ giant cells osteocl-like

adenosquamous

MORPHOLOGICAL HETEROGENETITY

Tumor type	Frequency	%	Type of associated IPMN	Median survival (months)
Conventional ductal adenocarcinoma	**91**	**51.4**	2 gastric	22.7
Combined ductal adenocarcinoma				
with cribriform component	17	9.6		28.7
with papillary component	17	9.6		13.9
with clear-cell component	16	9.0	1 pancreato-biliary	17.6
with complex component	12	6.7	1 gastric	10.7
with gyriform component	8	4.5		12.5
with micropapillary component	2	1.1		16.1
Variants and special carcinomas				
Adenosquamous carcinoma*	2	1.1		4.1
Colloidal/mucinous carcinoma*	2	1.1	1 intestinal	>64.3**
Medullary carcinoma*	1	0.5		>75.1**
Tubular carcinoma	3	1.7		>55.3**
Papillary carcinoma	6	3.4	2 pancreato-biliary, 1 intestinal, 1 gastric	20.6
All tumors	177	100		

NGS/IHC *KRAS/CDKN2A/SMAD4/TP53*

Schlitter *et al*. Sci reports 2017

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More frequent *MYC amplification*?

More frequent *GNAS mutation* ?

NGS/IHC *KRAS/CDKN2A/SMAD4/TP53*

No major difference

Schlitter *et al*. Sci reports 2017

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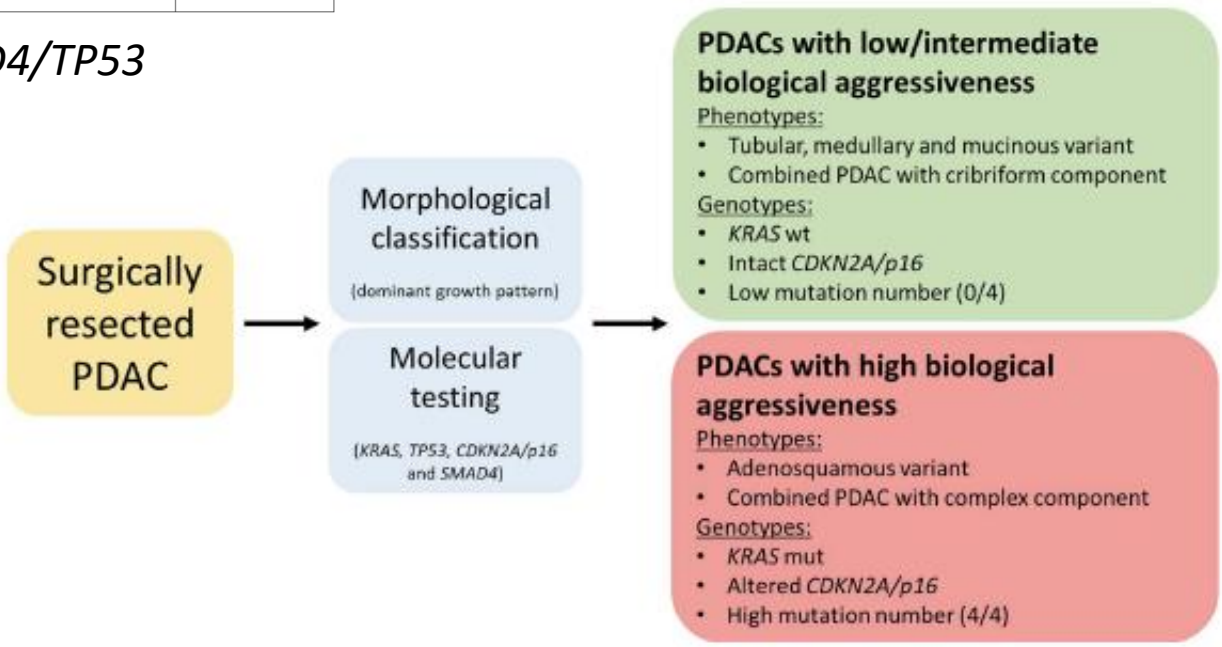


Schlitter *et al*. Sci reports 2017

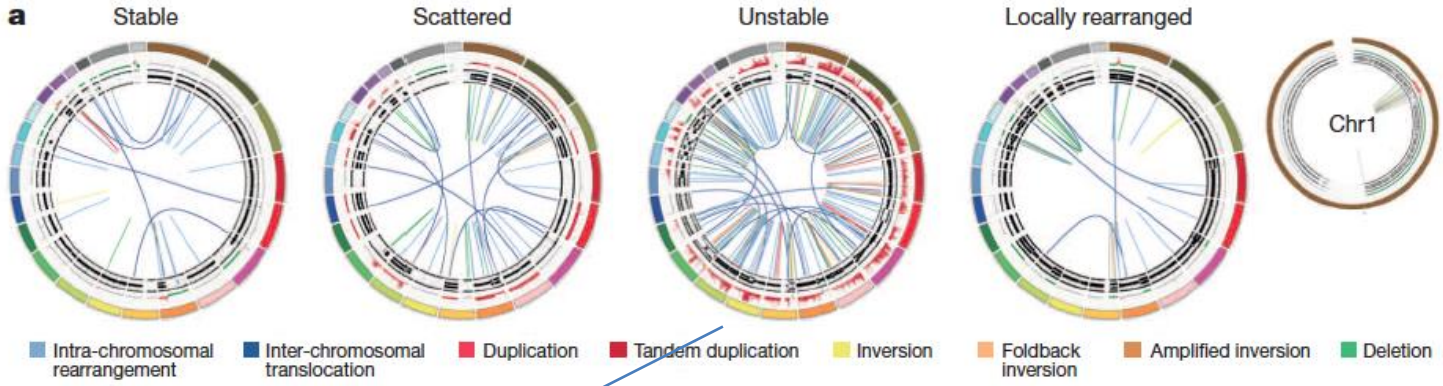
GENOMIC CARACTERIZATION

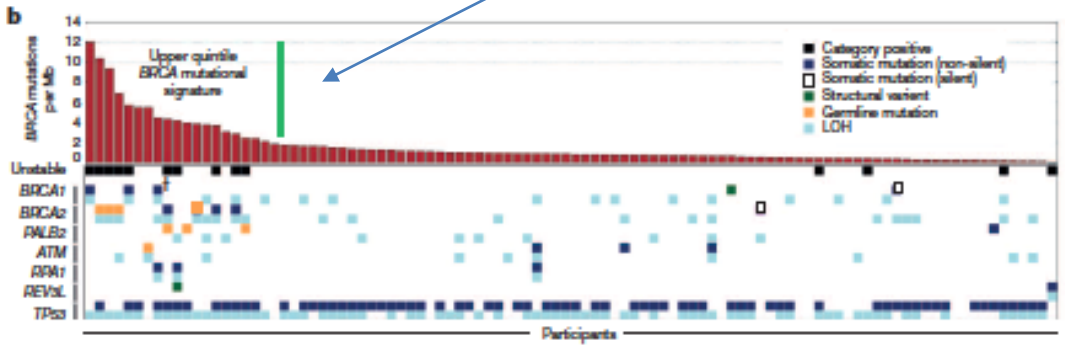
3 large datasets (ICGC (456 pts), TCGA (150 pts), Connor *et al.* (148 pts) – similar results

Connor *et al. JAMA Oncol 2016*

TCGA, Cancer cell 2017

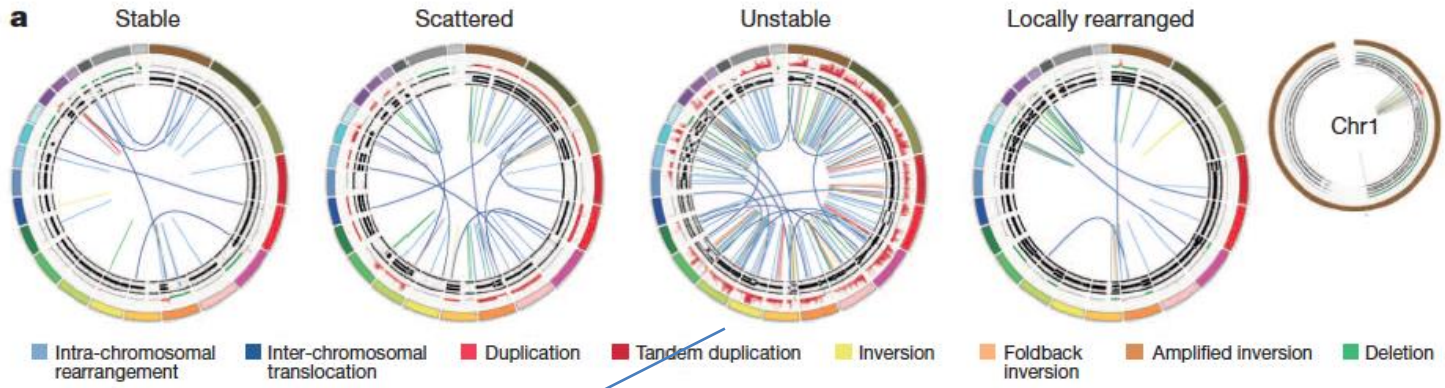
GENOMIC CARACTERIZATION

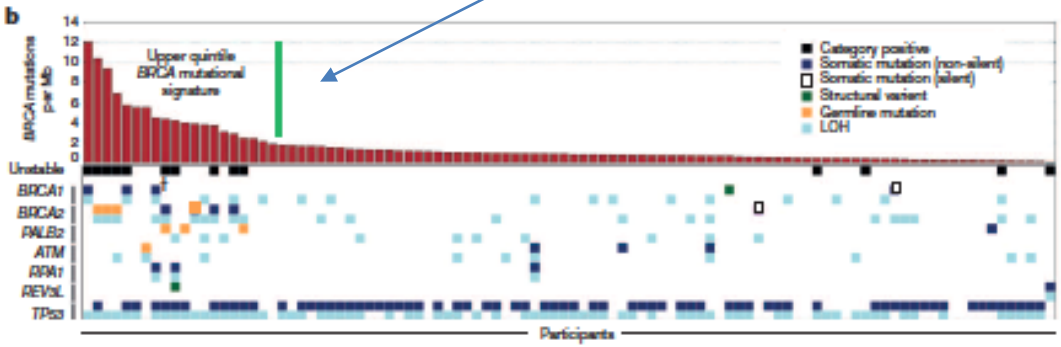




Waddell et a. Nature 2015

GENOMIC CARACTERIZATION





Signature	Discovery (n)	Replication (n)	ESPAC (n)	Population (%, 95% CI)
Age Related	115*	59	NA	69.9% (64.2-75.6%)
DSBR, total	17**	10	NA	10.8% (6.98-14.7%)
DSBR, germline	9	2	NA	4.42% (1.9-6.97%)
DSBR, somatic	2	2	NA	1.6% (0.045-3.2%)
DSBR, occult	6	6	NA	4.8% (2.2-7.5%)
MMR	4	0	6	1.7% (0.65-2.7%)
Signature 8	16	20	NA	14.5% (10.1-18.8%)
APOBEC	1***	4	NA	2.0% (0.27-3.8%)
Signature 17	1	2	NA	1.2% (0-2.56%)
Total sample sizes	154	95	342	NA

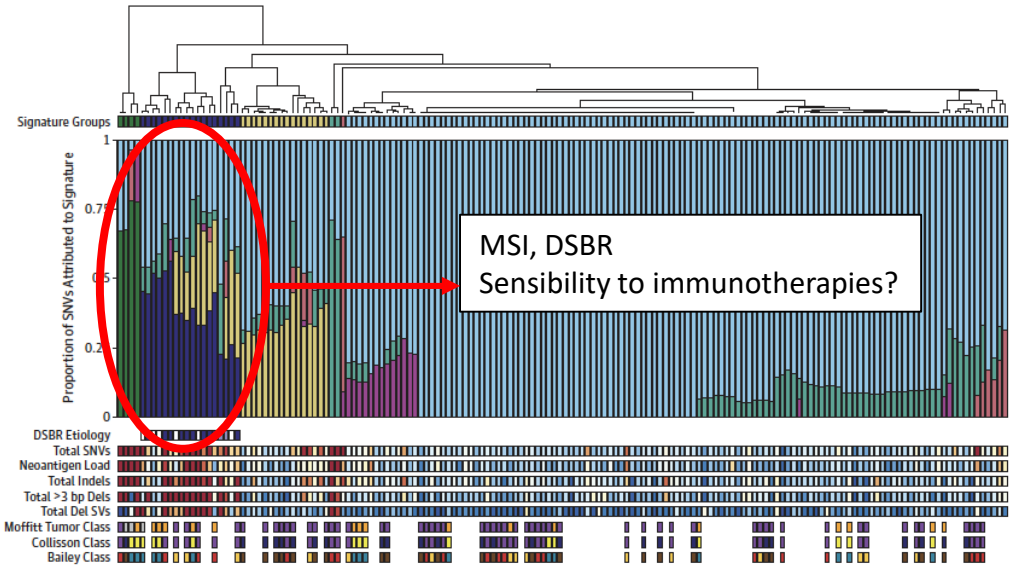
* there are 119 tumours from 115 cases in the Age Related discovery group
** there are 18 tumours from 17 cases in the DSBR discovery group
*** there are 2 tumours from 1 case in the APOBEC discovery group

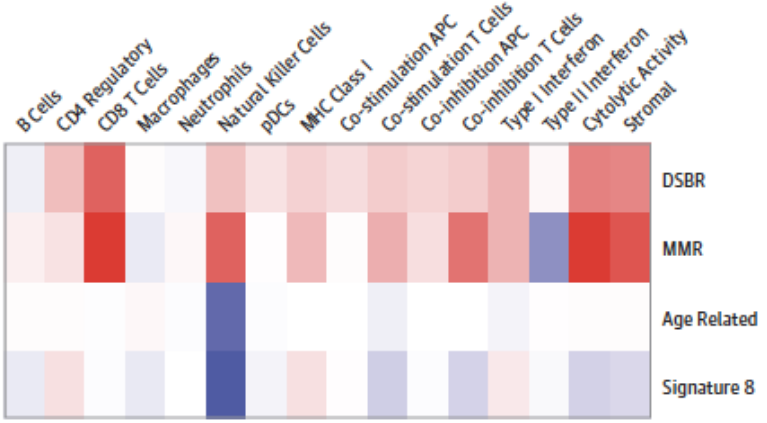
Benefit from PARPi in maintenance therapy (POLO trial)

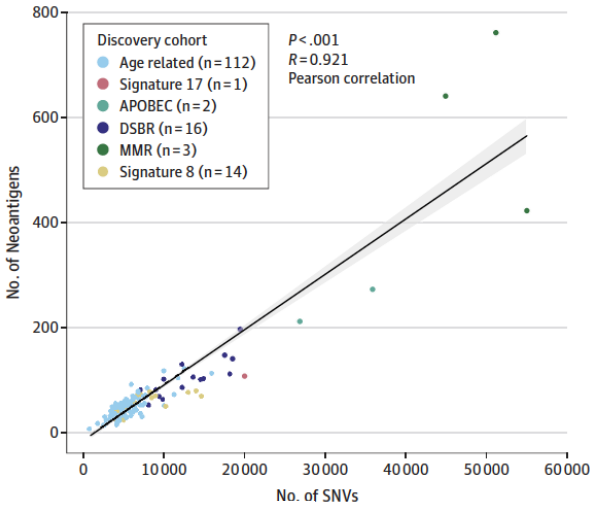
Waddell et a. Nature 2015

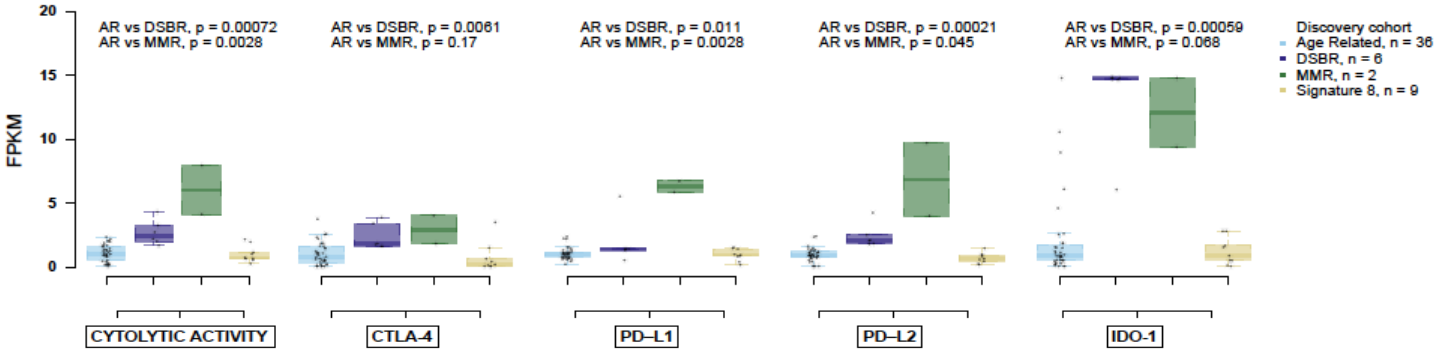
Connor *et al. JAMA Oncol 2016*

GENOMIC CARACTERIZATION





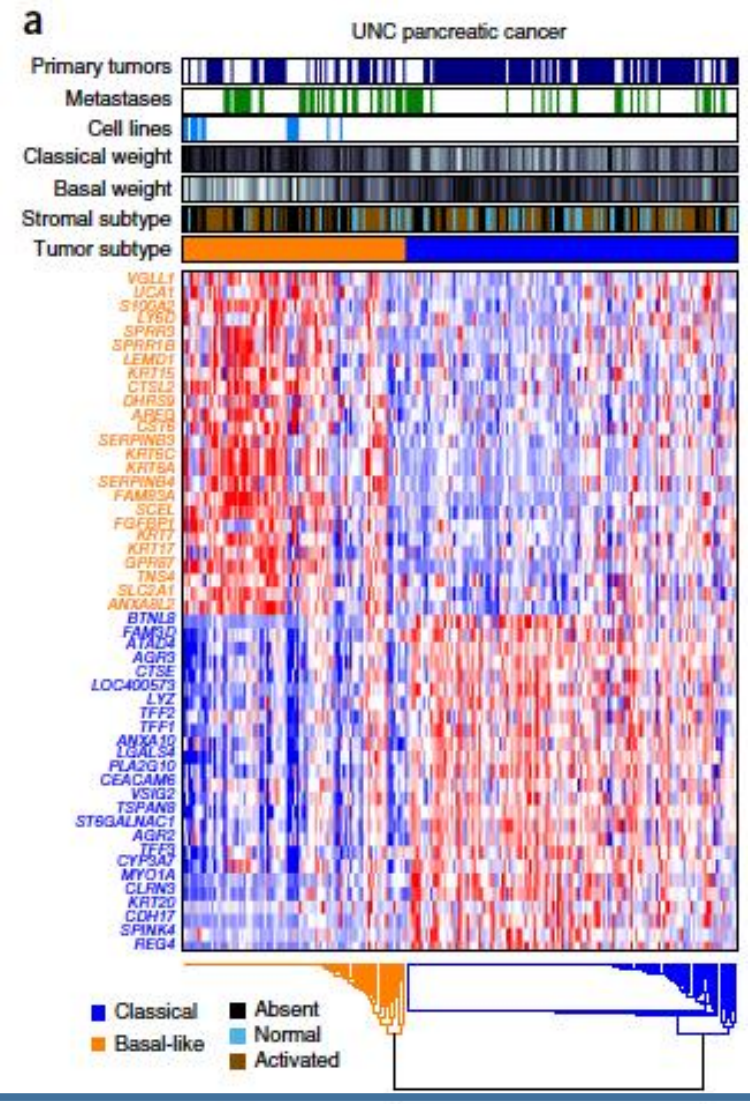




Connor *et al. JAMA Oncol 2016*

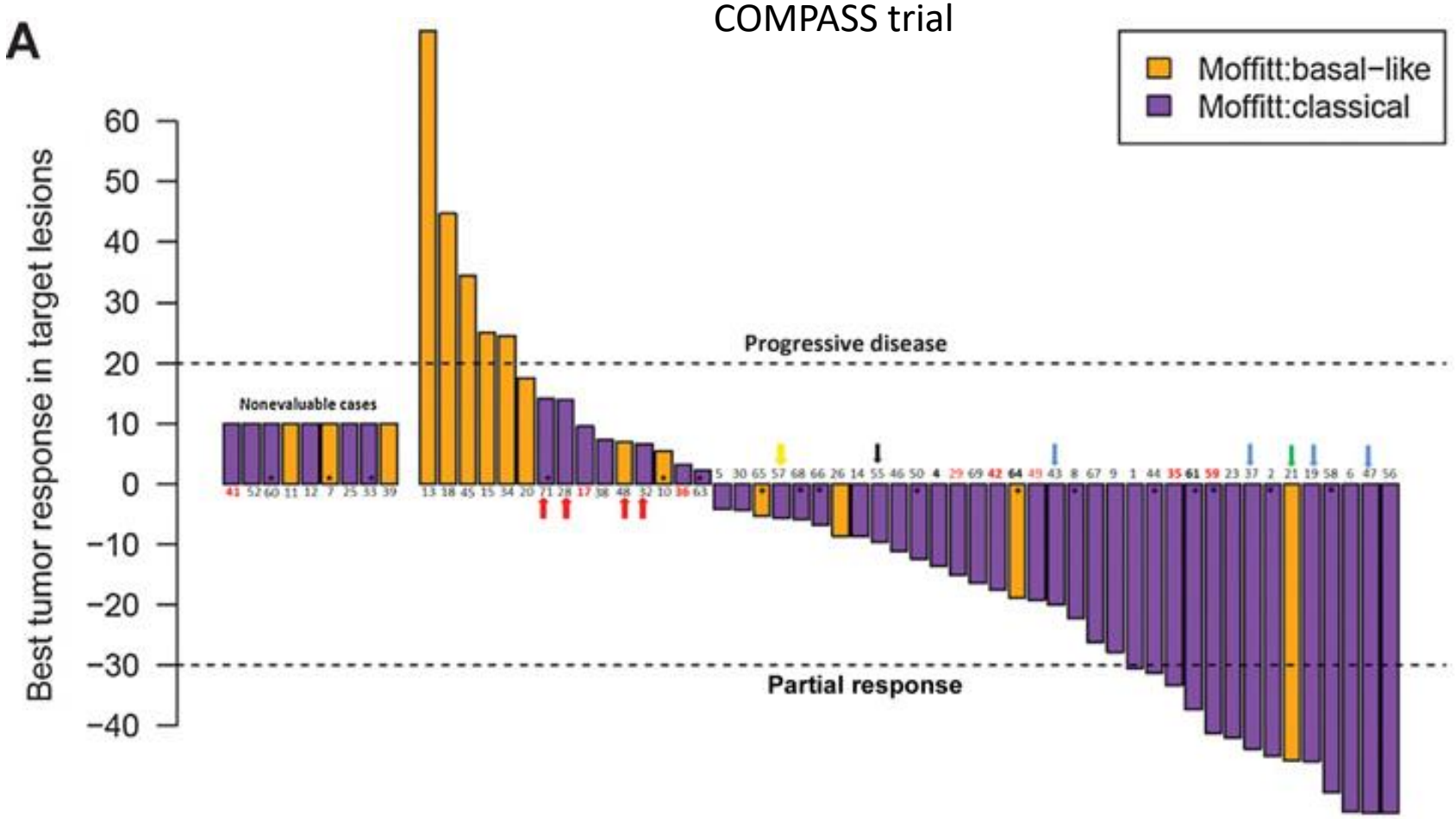
2 main transcriptomic tumor subtypes with different prognosis

Moffit *et al. Nat Gen* 2015



Molecular subtypes may have an important clinical utility++++

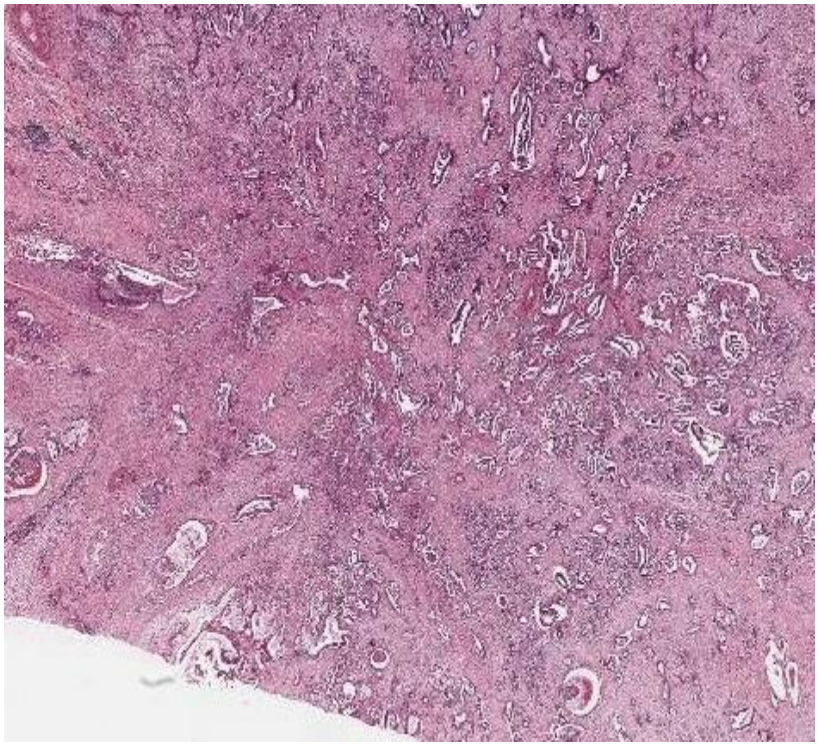
COMPASS trial

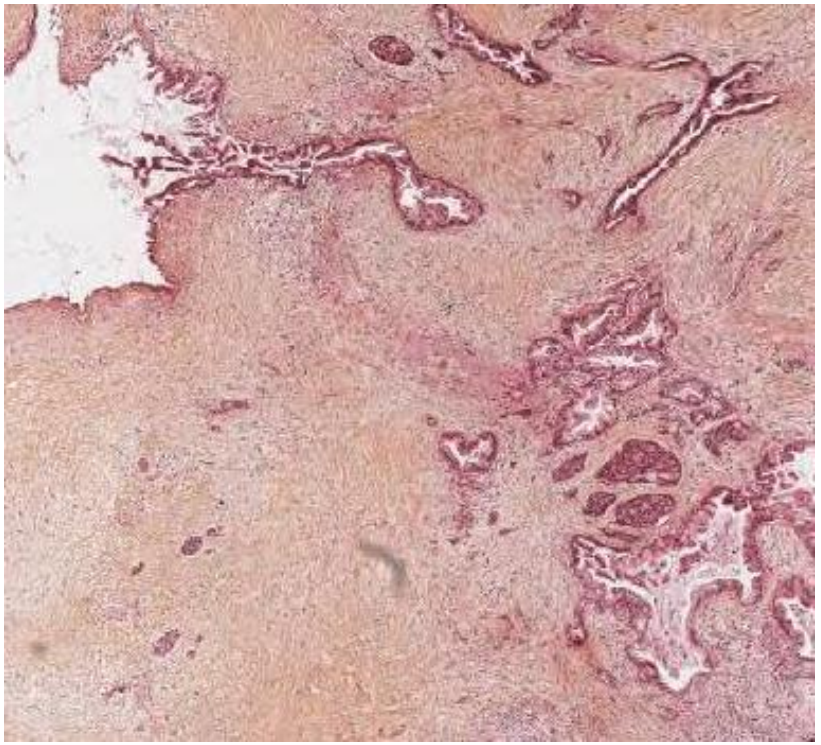


Aung *et al. Clin can res* 2018

TRANSCRIPTOMIC CHARACTERIZATION

True challenge! How to define (clearly) the molecular subtype in samples with few tumor cells???



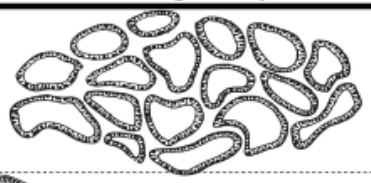


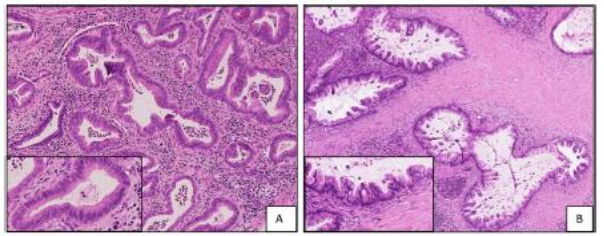
There is no routine tool available (RNA signature, immunohistochemistry etc…)

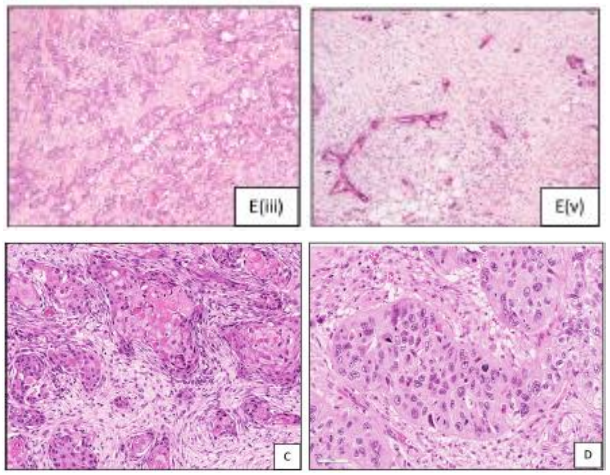
Algorythm from Noll *et al. Nat Med* 2015 not reproduced

Good old morphology may predict tumor subtypes…

A

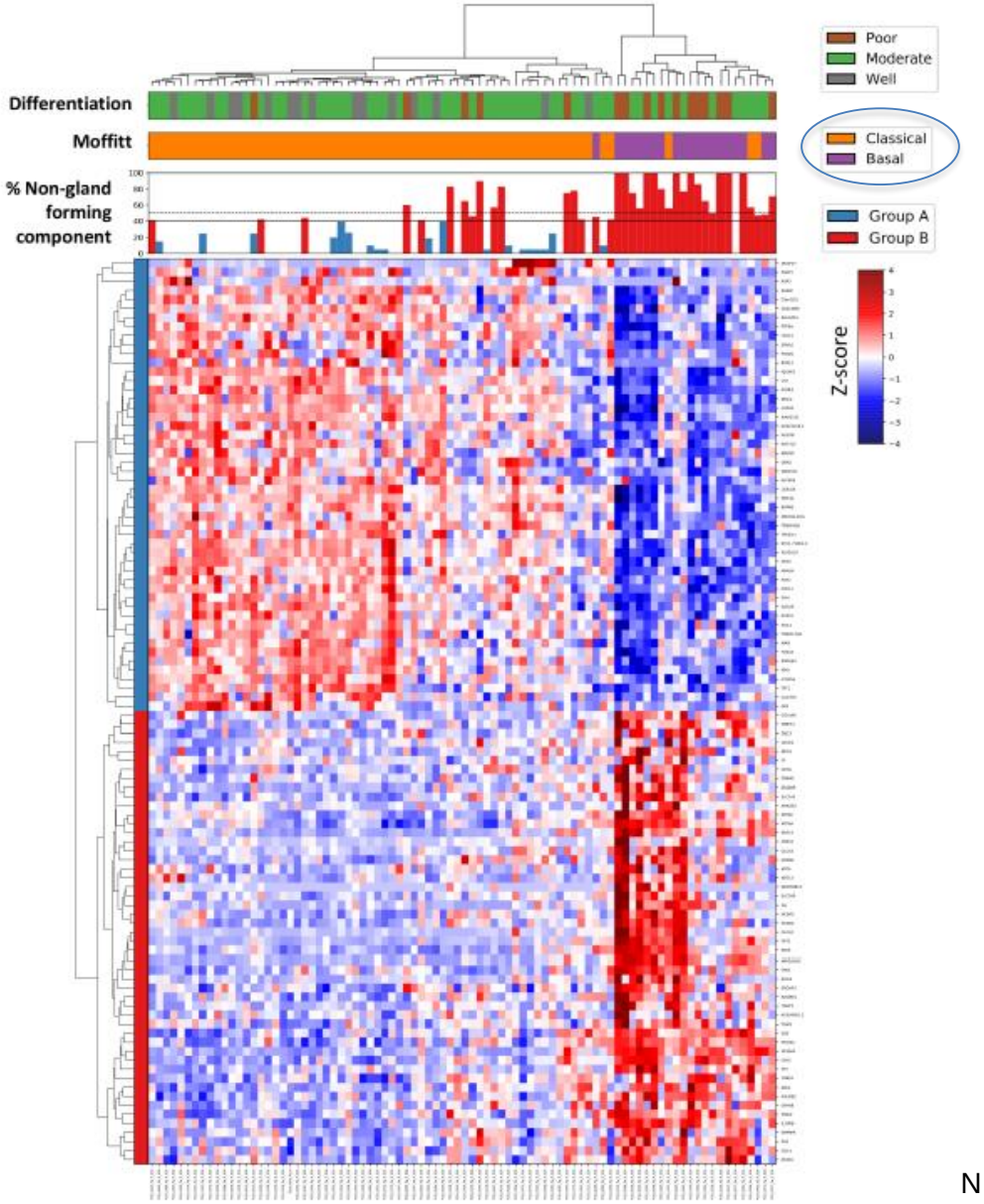
"Gland forming" component	Patterns
	Conventional
	Tubulopapillary
"Non-gland forming" component	**Patterns**
	Composite
	Squamous





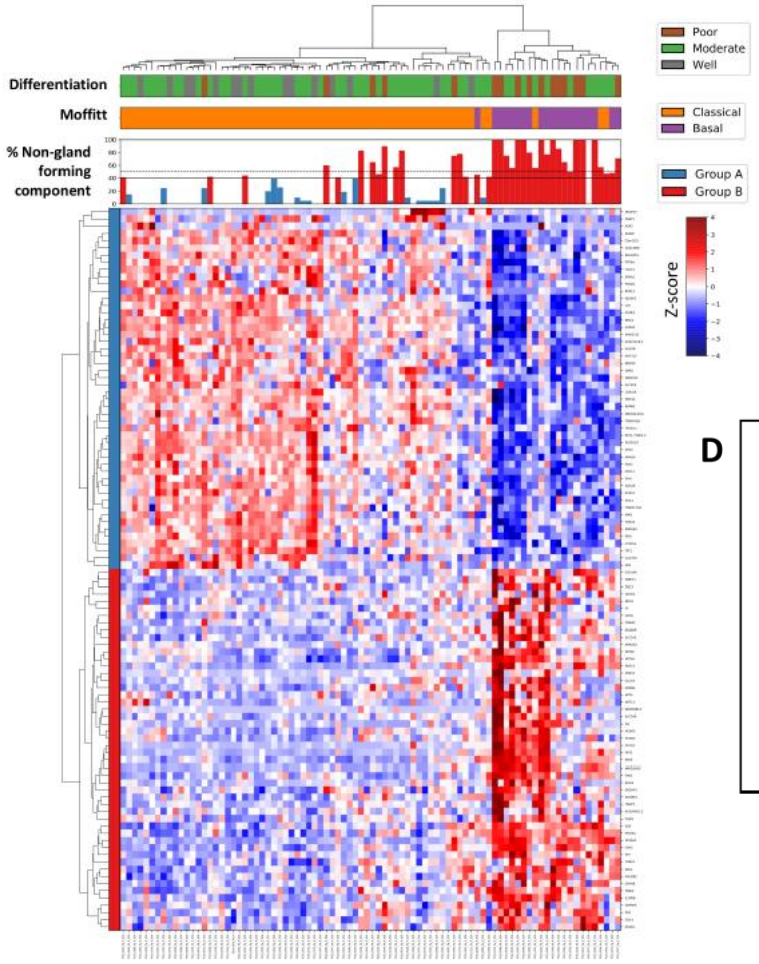
N Kalimuthu S, et al. Gut 2019

Good old morphology may predict tumor subtypes…

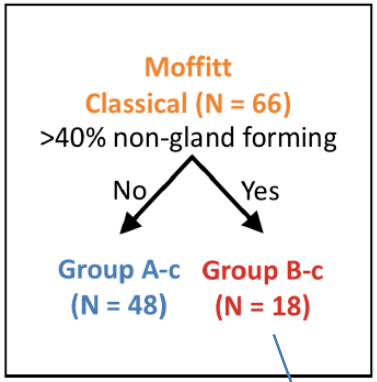


N Kalimuthu S, et al. Gut 2019

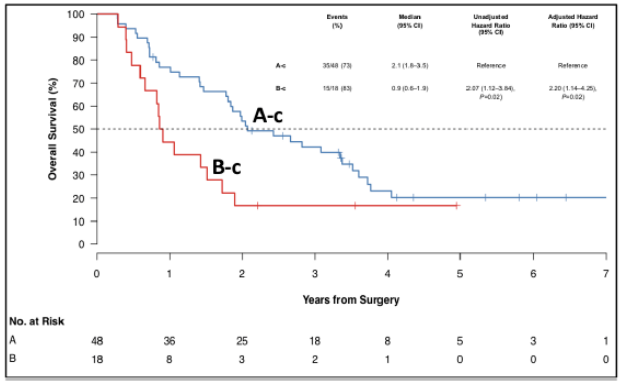
Good old morphology may predict tumor subtypes…



D



E

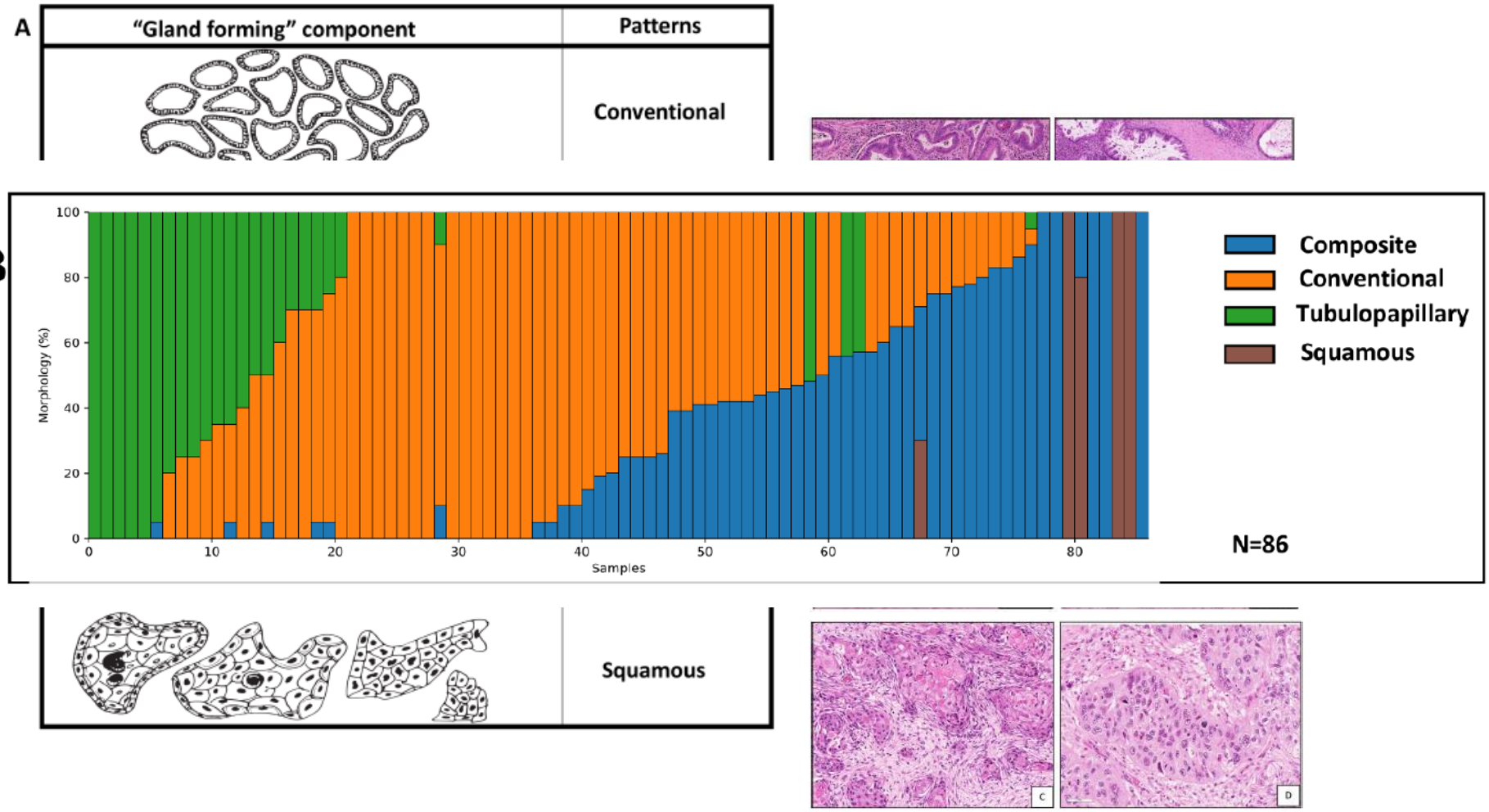


« classical » tumors with a basal like subpopulation?

N Kalimuthu S, et al. Gut 2019

TRANSCRIPTOMIC CHARACTERIZATION

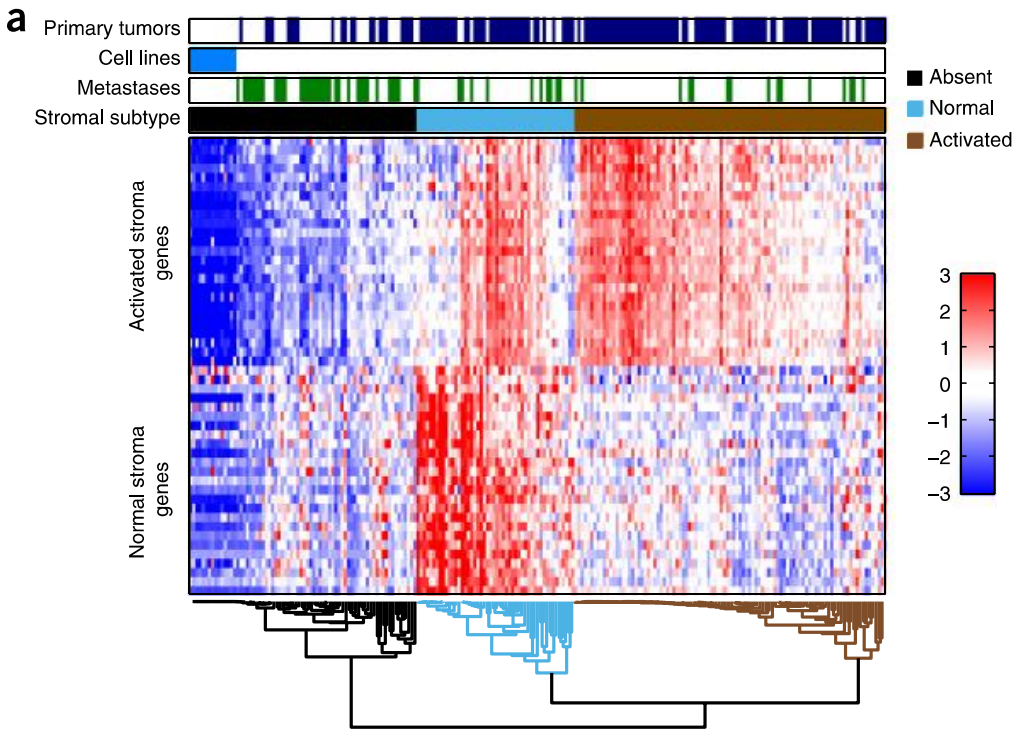
If tumor were pure, that would be too easy…..

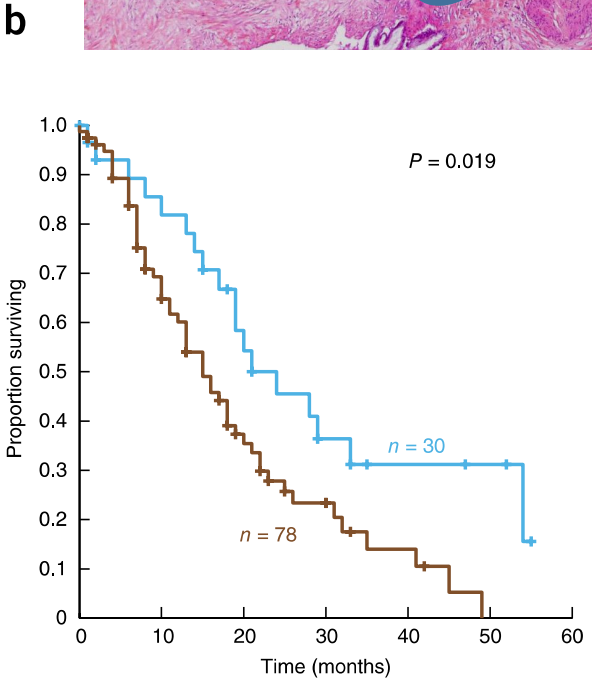


N Kalimuthu S, et al. Gut 2019

TRANSCRIPTOMIC CHARACTERIZATION

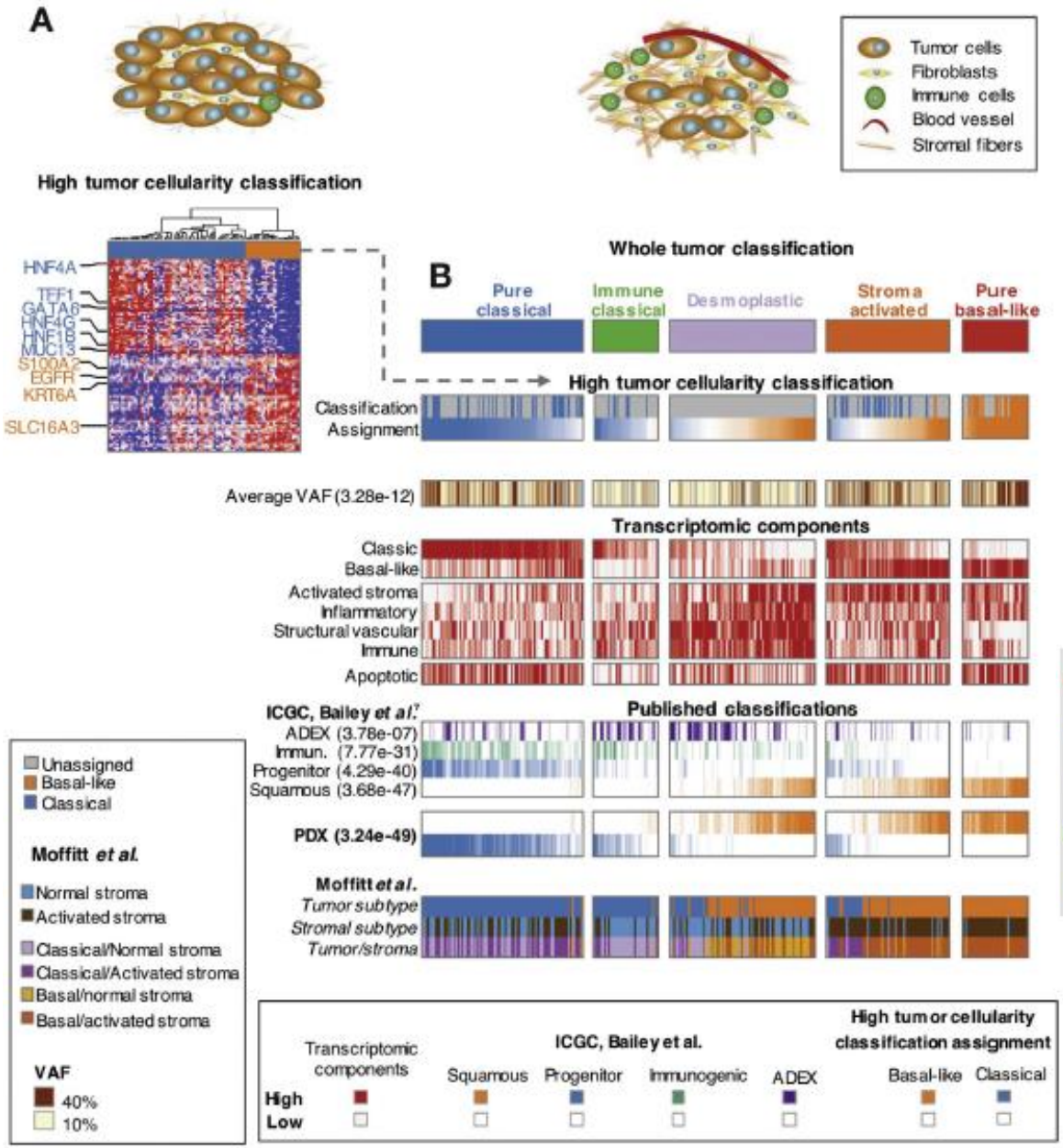
And the stroma is also heterogeneous…

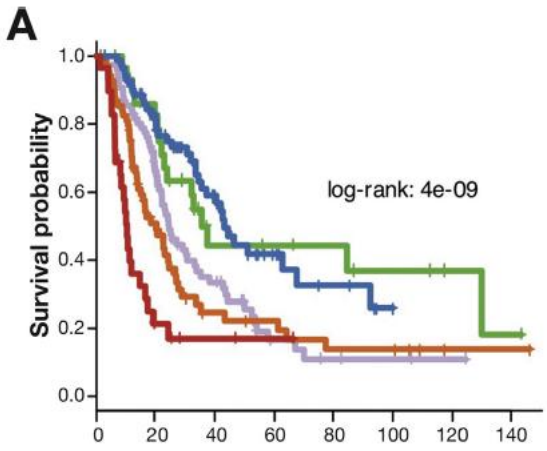


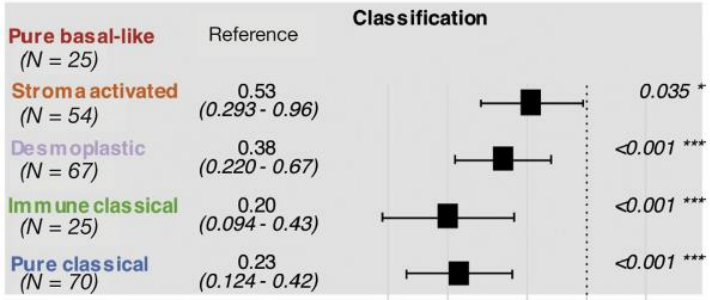


Moffitt et al. Nature genetics 2015

TRANSCRIPTOMIC CHARACTERIZATION



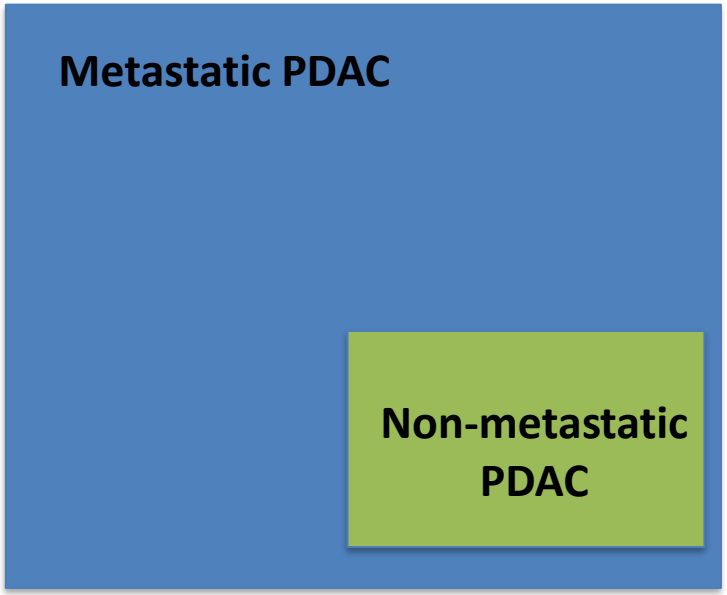




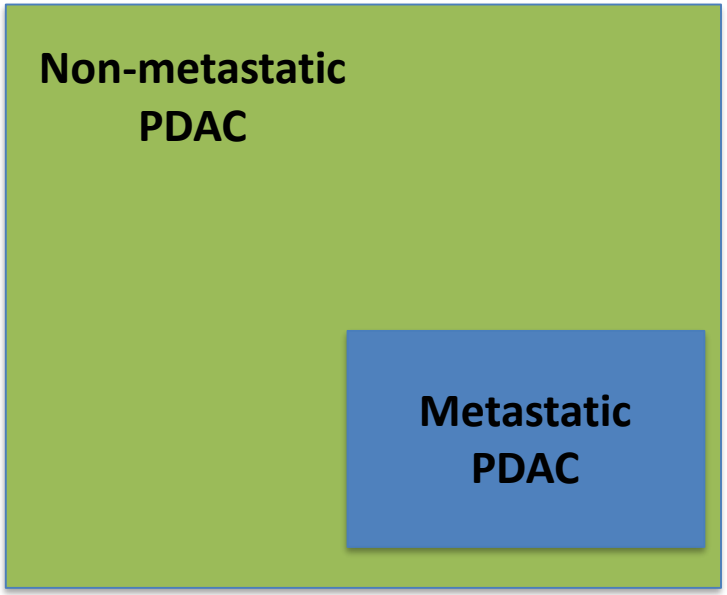
NO CONSENSUS ON THE STROMA YET!

Puleo *et al, Gastroenterology* 2018

MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA

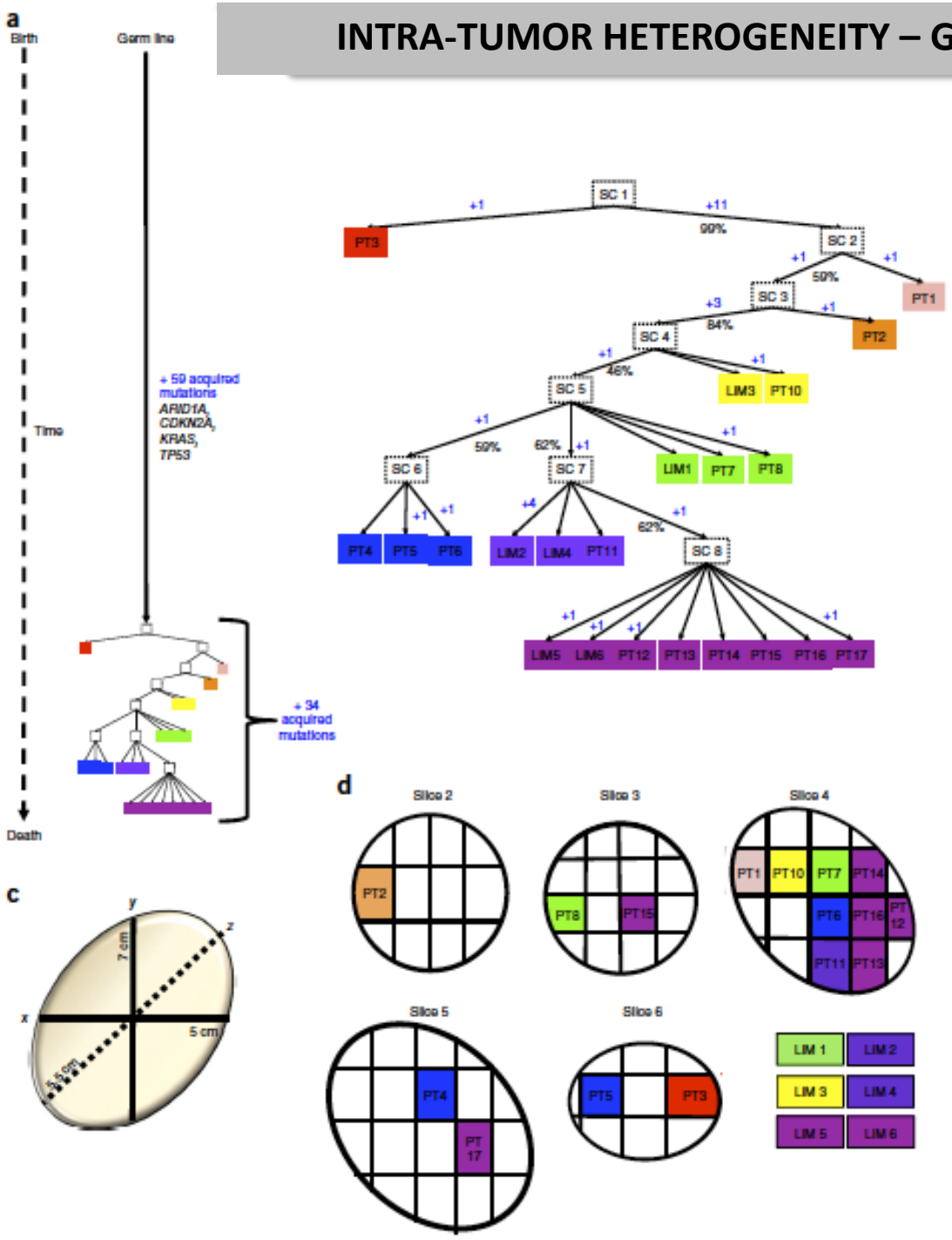


What we treat….



What we know (biology)….

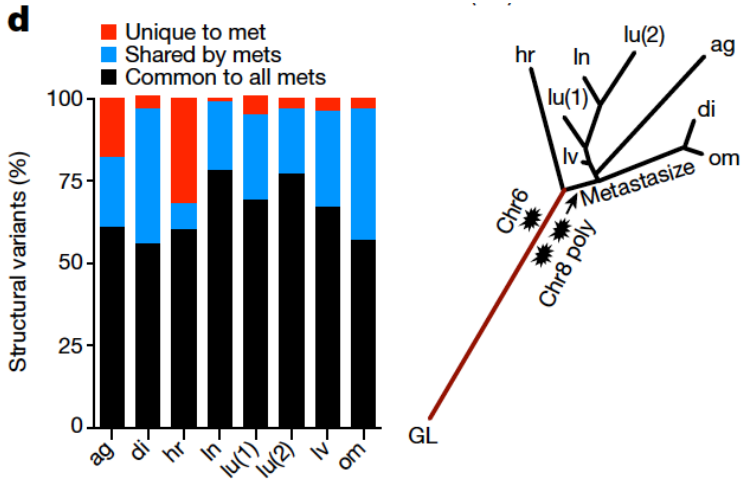
INTRA-TUMOR HETEROGENEITY – GENOMIC LEVEL



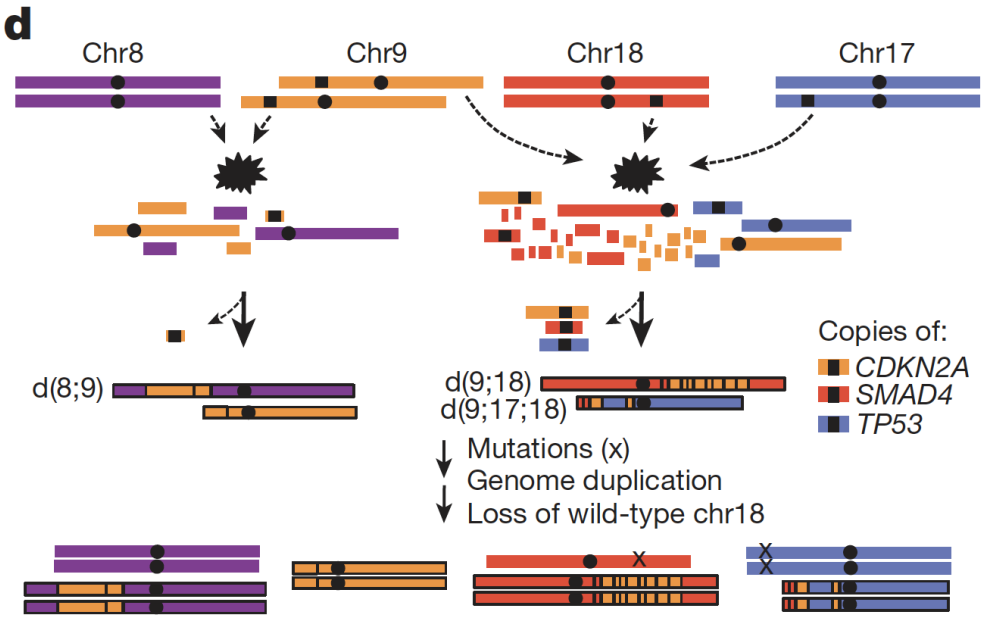
- **Low heterogeneity of classical driver genes**
- **Most genomic events happen early**
- **No « mestastasis » gene**
- **Physical and genomic spatialisation are different+++**

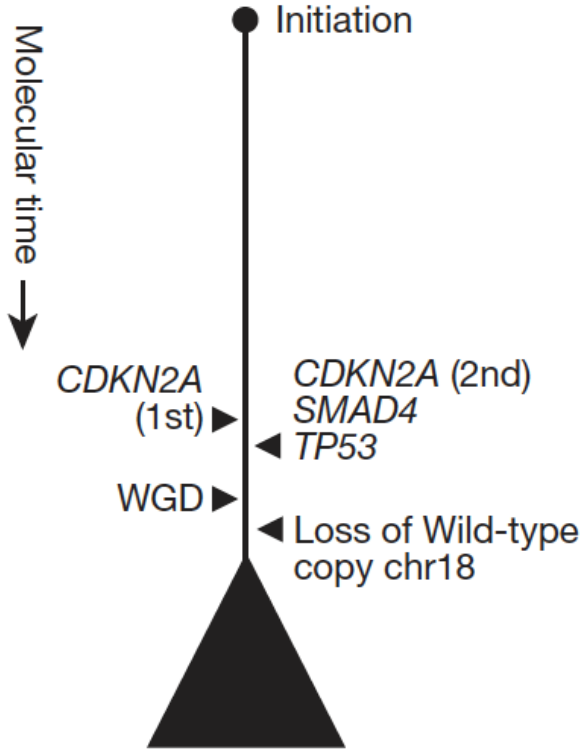
Makohon-Moore *et al. Nat Gen* 2017
Yachida *et al. Nature* 2010

INTRA-TUMOR HETEROGENEITY – GENOMIC LEVEL



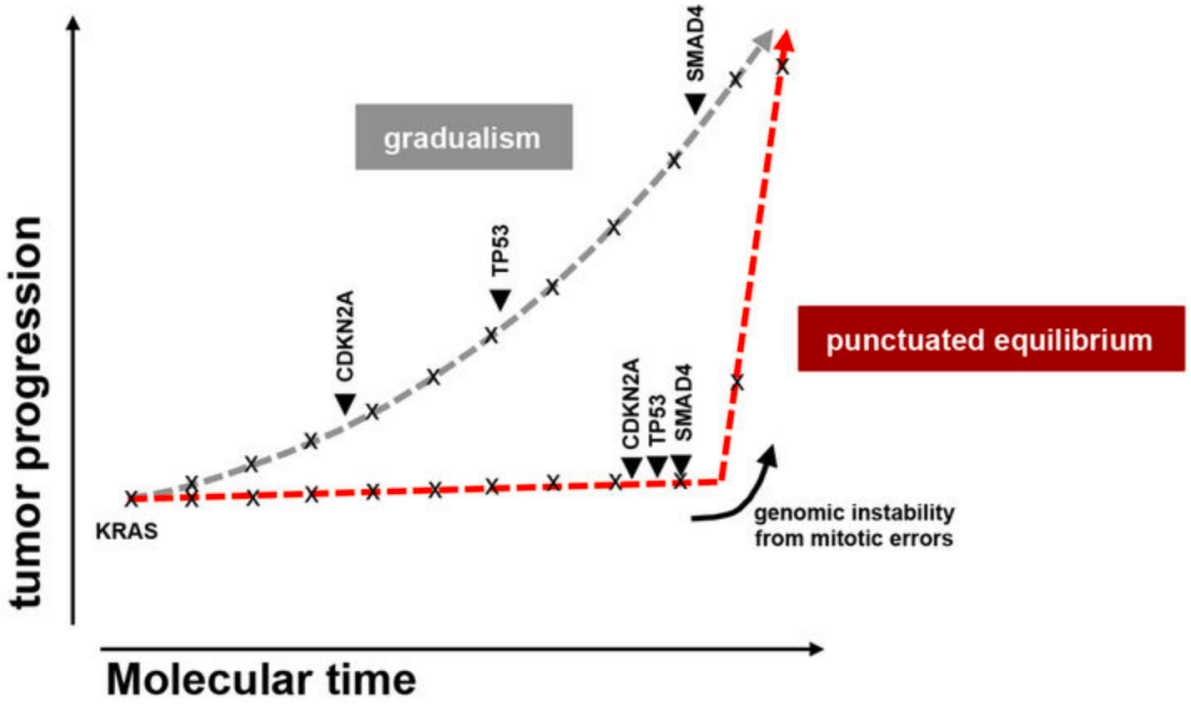
- Most genomic events happen before the first metastase
- 50% of tumeurs are not diploïd (T ou H)
- Multiples simultaneous genomic alterations

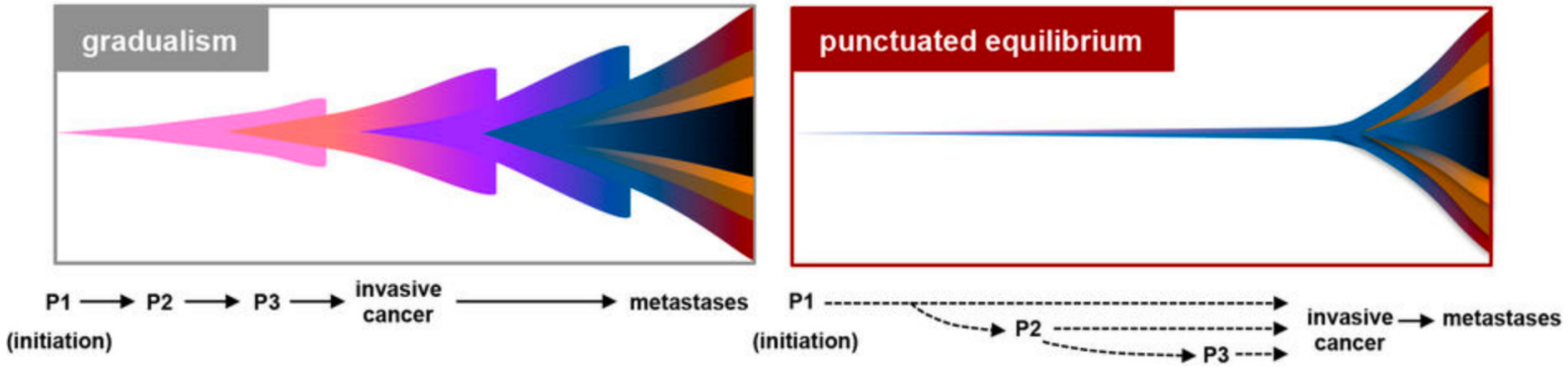




Notta *et al. Nature* 2016

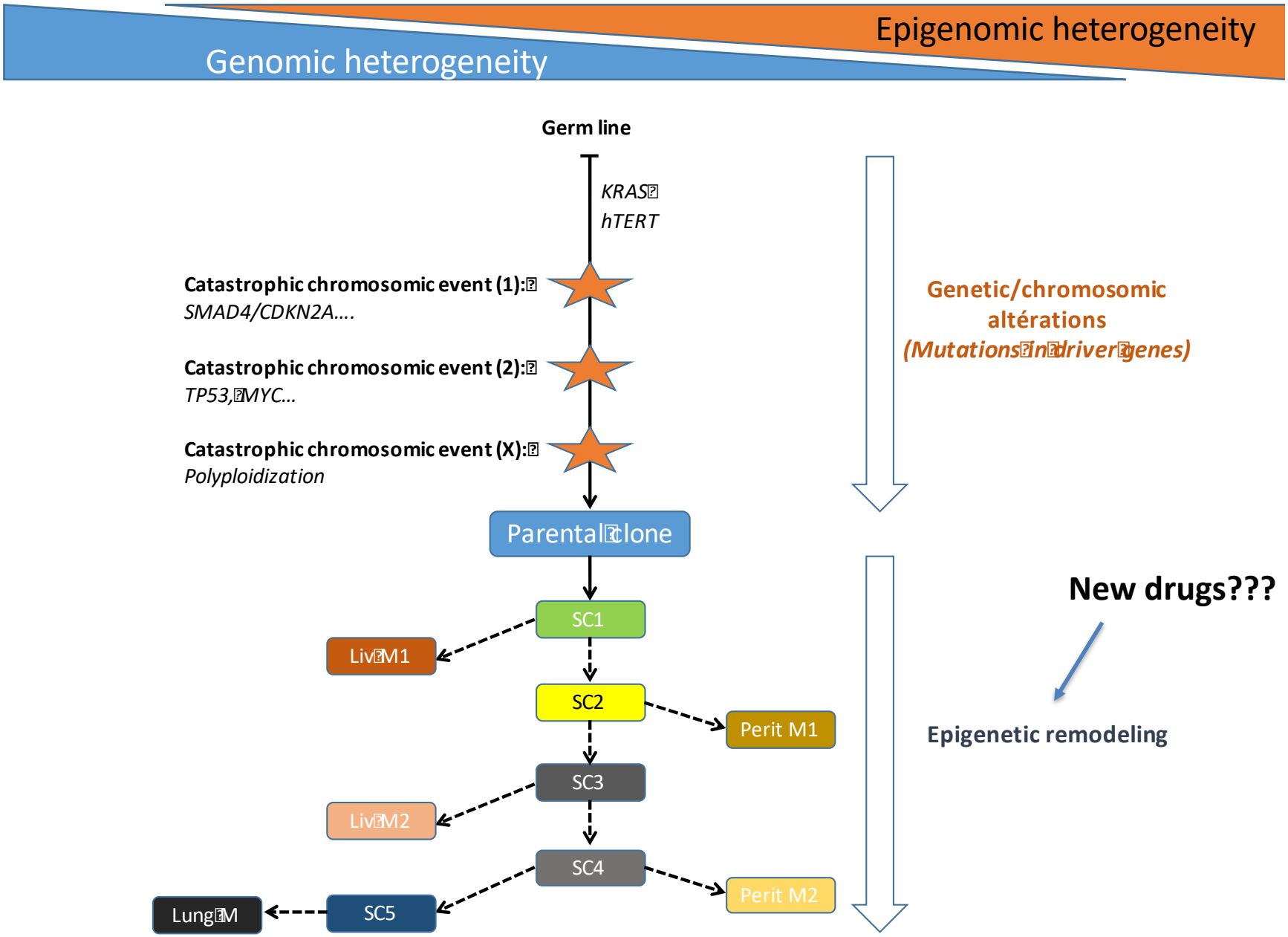
How to follow high risk patients???





Notta *et al. Nature* 2016

INTRA-TUMOR HETEROGENEITY - EPIGENOMIC



Pancreatic adenocarcinoma – hereditary forms

JAMA | Original Investigation

Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer

Chunling Hu, MD, PhD; Steven N. Hart, PhD; Eric C. Polley, PhD; Rohan Gnanaolivu, BS; Hermela Shimelis, PhD; Kun Y. Lee, PhD; Jenna Lilyquist, PhD; Jie Na, MS; Raymond Moore, BS; Samuel O. Antwi, PhD; William R. Bamlet, MS; Kari G. Chaffee, MS; John DiCarlo, PhD; Zhong Wu, PhD; Raed Samara, PhD; Pashtoon M. Kasi, MD; Robert R. McWilliams, MD; Gloria M. Petersen, PhD; Fergus J. Couch, PhD

- Mayo Clinic, 2000-2016
- Case control study:
- 3030 adults FamPa, 123 000 control subjects

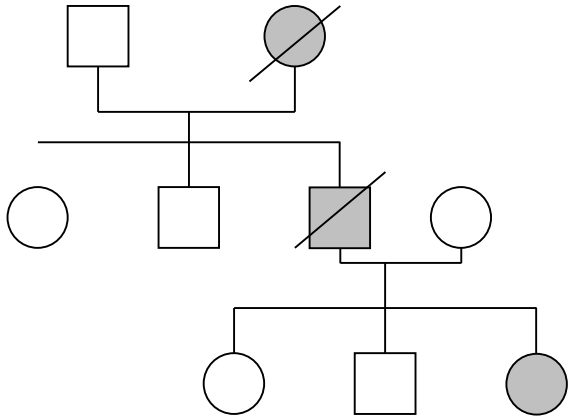
Table 3. Comparisons of Mutation Carriers by Panel Gene Between Pancreatic Cancer Cases and gnomAD Controls

	Cases			gnomAD Controls			Cancer Risk[a]	
Genes	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.

Who should we screen?

Multiple cases within a family
(genes?)



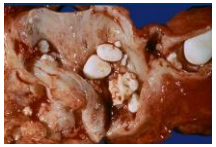
Genetic syndrome

BRCA 2

Familial melanoma
(CDKN2A/p16))

+ 1 PDAC case in the family

Peutz-Jeghers
(STK11/LKB1)



Hereditary Pancreaticis
(PRSS1)

Theoretical PDAC risk ≥ 5-10%

Hereditary Pancreatic Cancer predisposition syndromes, their genetic findings and lifetime risk of pancreatic cancer by the age of 70

Syndrome	Gene	Cumulative risk of pancreatic cancer at age 70
PJS	STK11	20-60%
Hereditary Pancreatitis	PRSS1/ SPINK1	40%
FAMMM	CDKN2A/p16	17%
HBOC	BRCA1, BRCA2	3-8%
ATM	ATM	5 %
Cystic fibrosis	CFTR	<5%
Lynch Syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	<5%
Li Fraumeni	TP53	<5%
FAP	APC	2%

PJS – Peutz-Jeghers-Syndrome, FAMMM – familial atypical multiple mole melanoma,
HBOC – hereditary breast and ovarian cancer, ATM –Ataxia teleangiectasia)

Who should we screen?

VOLUME 35 · NUMBER 30 · OCTOBER 20, 2017

JOURNAL OF CLINICAL ONCOLOGY | RAPID COMMUNICATION

Deleterious Germline Mutations in Patients With Apparently Sporadic Pancreatic Adenocarcinoma

Koji Shindo, Jun Yu, Masaya Suenaga, Shahriar Fesharakizadeh, Christy Cho, Anne Macgregor-Das, Abdulrehman Siddiqui, P. Dane Witmer, Koji Tamura, Tae Jun Song, Jose Alejandro Navarro Almario, Aaron Brant, Michael Borges, Madeline Ford, Thomas Barkley, Jin He, Matthew J. Weiss, Christopher L. Wolfgang, Nicholas J. Roberts, Ralph H. Hruban, Alison P. Klein, and Michael Goggins

Overall: 35/834 (4.2%)

BRCA2: 12
ATM: 10
BRCA1: 3
PALB2: 2
MLH1: 1
CDKN2A:1
TP53:1

Table 2. Patient Characteristics

Classification	Pancreatic Cancer, No. (%)	Other Diseases, No. (%)
Total no. of patients	854	339
Mean age in years ± SD	65.0 ± 10.9	60.1 ± 14.1
< 51	81 (9)	79 (23)
51-60	199 (23)	80 (24)
61-70	297 (35)	95 (28)
71-80	220 (26)	69 (20)
≥ 80	57 (7)	16 (5)
Sex		
Male	455 (53)	181 (53)
Female	399 (47)	158 (47)
Race		
White	756 (89)	280 (83)
African American	52 (6)	31 (9)
Other	46 (5)	28 (8)
Family history of pancreatic cancer	109 (12.7)	15 (4)
First-degree relative with pancreatic cancer	77 (9.0)	

Who should we screen?

- **Familial / personnal history of neoplasia compatible with a genetic syndrome**
    - Individuals with three or more affected blood relatives, with at least one affected
    - Individuals with at least two affected FDRs with PC, with at least one affected FDR
    - *BRCA2/CDKN2A/PALB2* mutation carriers with one affected FDR
    - Hereditary pancreatitis
    - Peutz-Jeghers

- **Excellent response to Pt-based treatment (to be proven)**
    - Prolonged survival (many other reasons!!!)

TAKE HOME MESSAGES

- **Pancreatic adenocarcinoma**
  - **Rising incidence**
  - **Role of systemic inflammation / metabolic syndrome**

- **Low heterogeneity at the mutational level**
- **High heterogeneity (space and time) at the epigenetic/transcriptomic level**

- **2 main tumor subypes with different prognosis**
  + X stroma subtypes… = Y PDAC subtypes!

- **Germline mutation (5-8%) (BRCA2/1++, MSI 1% max)**