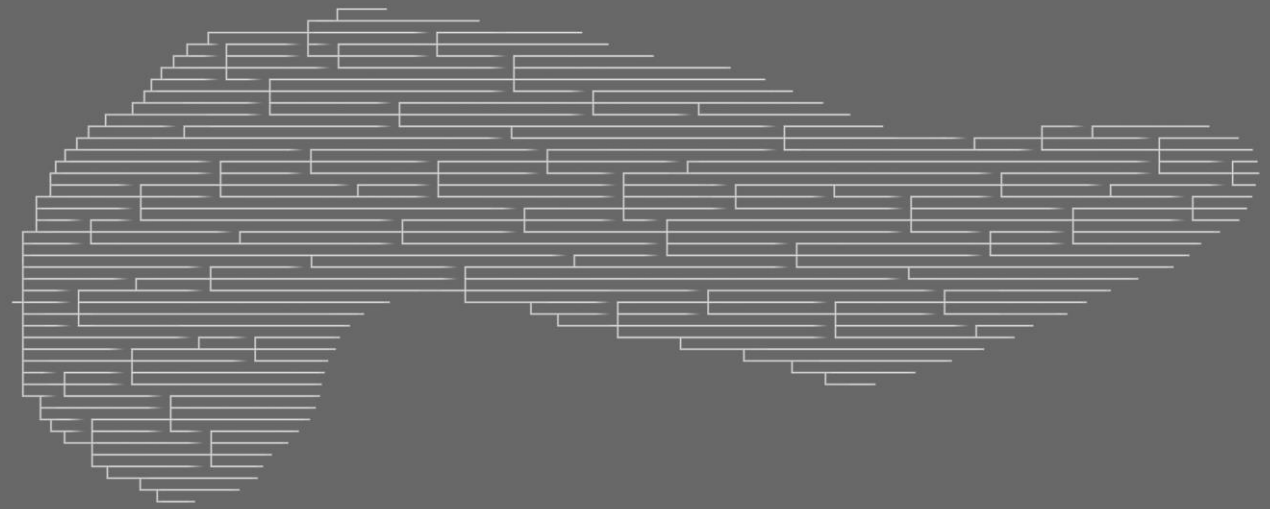
Genetics of Pancreatic Cancer



Michaël Noë

Resident, UMC Utrecht, The Netherlands

Post-doctoral Research Fellow, Johns Hopkins University, USA

WHO: 5th edition

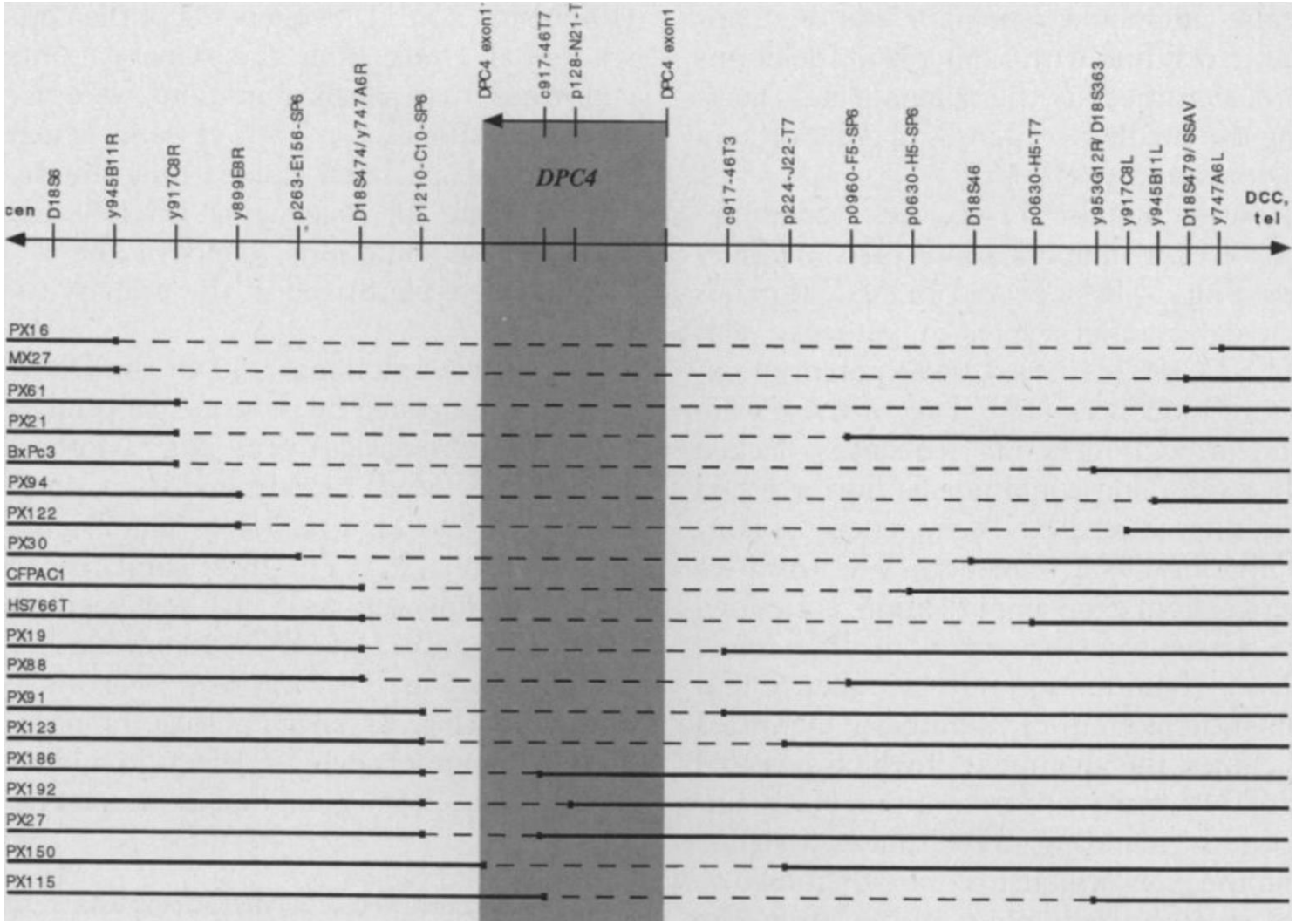
Diagnostic molecular pathology
Not clinically relevant

History of the genetics of pancreatic cancer

- 1982: KRAS discovered in pancreatic cancer cell lines
  - Similarities with Rous Sarcoma Virus
- 1995: DPC1 & DPC2 discovered (later: BRCA2)
  - ‘Deleted in Pancreatic Cancer’
  - Finding spots of homozygous deletions in cancer cell lines (RDA)
- 1994: DPC3 discovered (later: P16, CDKN2A)
- 1996: DPC4 discovered (later: SMAD4)

DPC: Deleted in Pancreatic Cancer; RDA: Representational Difference Analysis

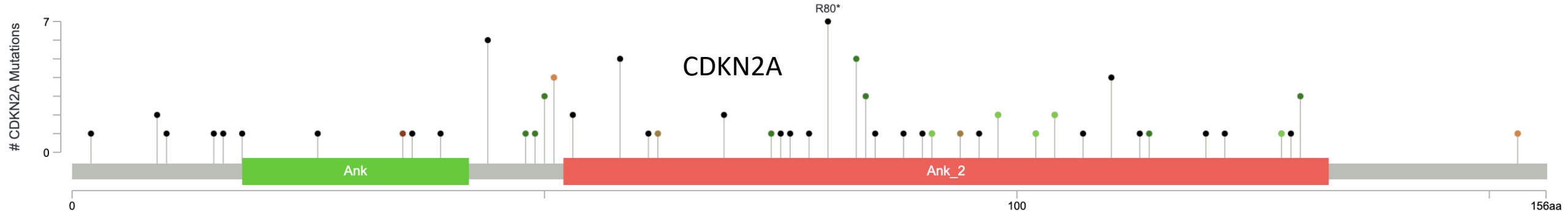
DPC: Deleted in Pancreatic Cancer



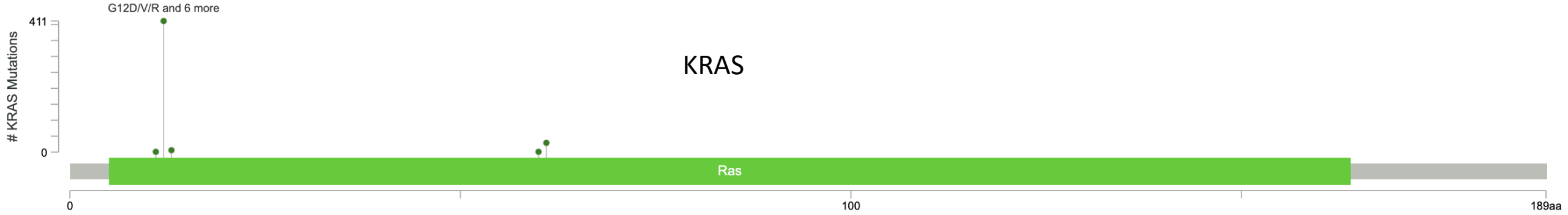
Hahn et al. DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. Science. 1996

Tumor Suppressors vs. Oncogenes

- Tumor suppressors (CDKN2A, TP53, SMAD4)
  - many ways to break them (chaos = more entropy)



- Oncogenes (KRAS)
  - Only a couple of ways to make it work better / more (structure = less entropy)

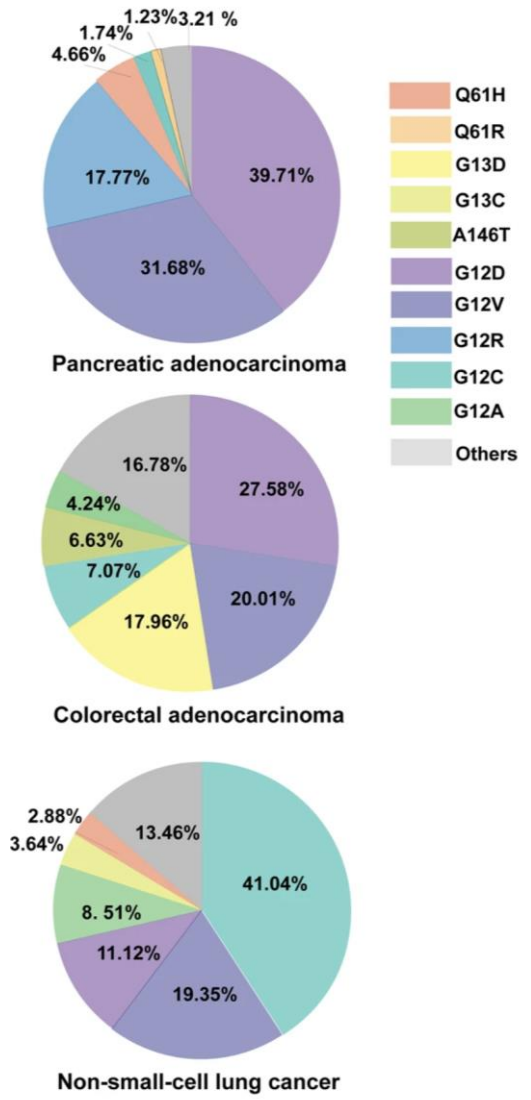


Pancreatic cancer: driver genes

- KRAS
- CDKN2A (P16)
- TP53
- SMAD4 (immunohistochemistry – if it works)

Pancreatic cancer: driver genes

- KRAS
- CDKN2A (P16)
- TP53
- SMAD4



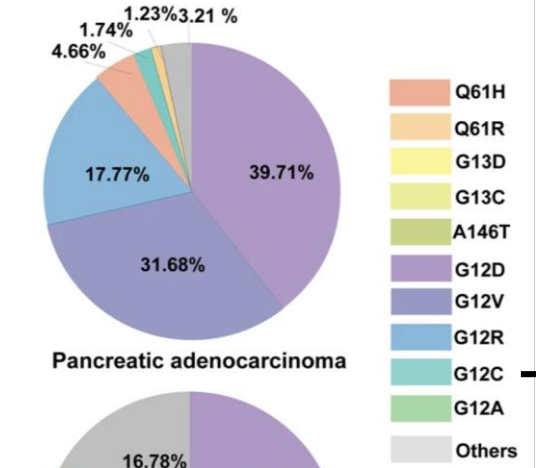
Different KRAS-mutations in different cancers: reflection of different impact of carcinogens

- Smoking (C>A)
- Bacteria
- Aging
- APOBEC
- etc…

Alexandrov LB et al. The repertoire of mutational signatures in human cancer. Nature. 2020

Pancreatic cancer: driver genes

- KRAS
- CDKN2A (P16)
- TP53
- SMAD4

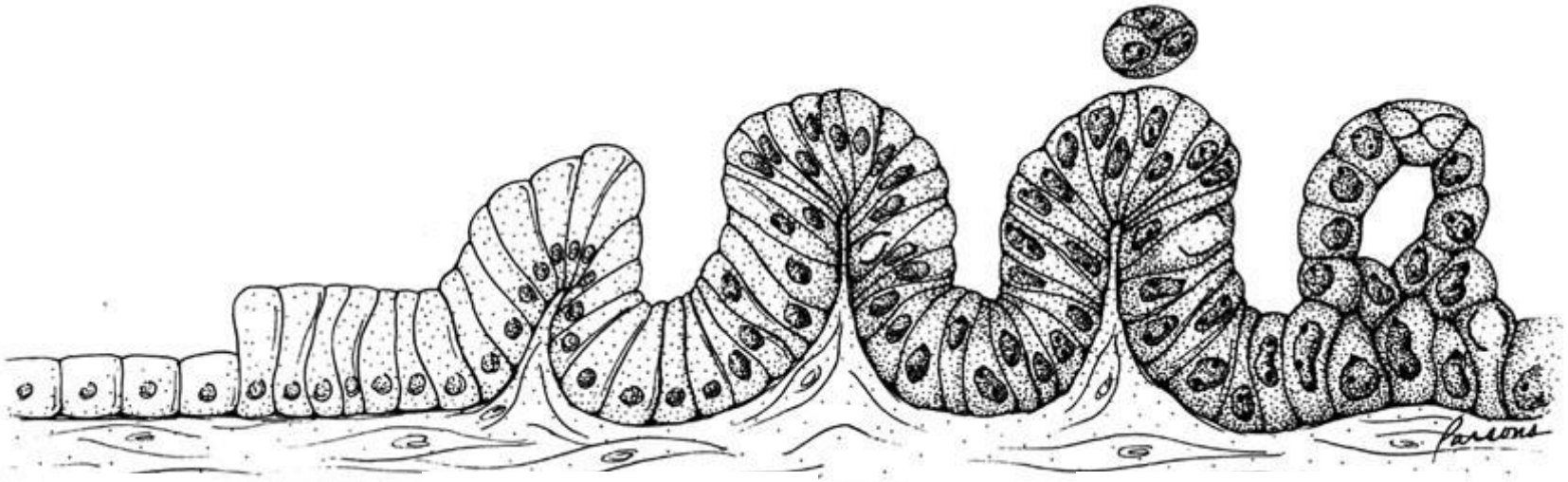


→ Sotorasib: irreversible inhibitor of KRAS G12C (1-2%)

- ASCO 2022: CodeBreaK100 study showed effect of the therapy in pancreatic cancer patients
  - Partial response: 21%
  - Disease control: 84%

From precursor to carcinoma (PDAC)

- Deciphering the pathogenesis:



Precursors to pancreatic ductal adenocarcinoma (PDAC)

Precursor	Malignant	Mutations
PanIN	PDAC	KRAS, CDKN2A, TP53, SMAD4
IPMN	PDAC-light	KRAS, GNAS, CDKN2A, RNF43, TP53, SMAD4
IOPN	PDAC-light	Fusions between ATP1B1 / DNAJB1 and PRKACA / PRKACB
MCN	PDAC-light	KRAS, CDKN2A, RNF43, TP53, SMAD4
ITPN	PDAC	PIK3CA, PTEN, KMT2A, KMT2B, KMT2C, FGFR2 fusions
SCAdenoma	SCAdenocarcinoma?	VHL
	SPN	CTNNB1
	Acinar Cell Carcinoma	BRCA2, CHEK2, FAT

PanIN: Pancreatic Intraepithelial Neoplasia
PDAC: Pancreatic Ductal Adenocarcinoma
IPMN: Intraductal Papillary Mucinous Neoplasm
IOPN: Intraductal Oncocytic Papillary Neoplasm
MCN: Mucinous Cystic Neoplasm
ITPN: Intraductal Tubulopapillary Neoplasm
SCAdenoma: Serous Cystadenoma
SPN: Solid Pseudopapillary Neoplasm

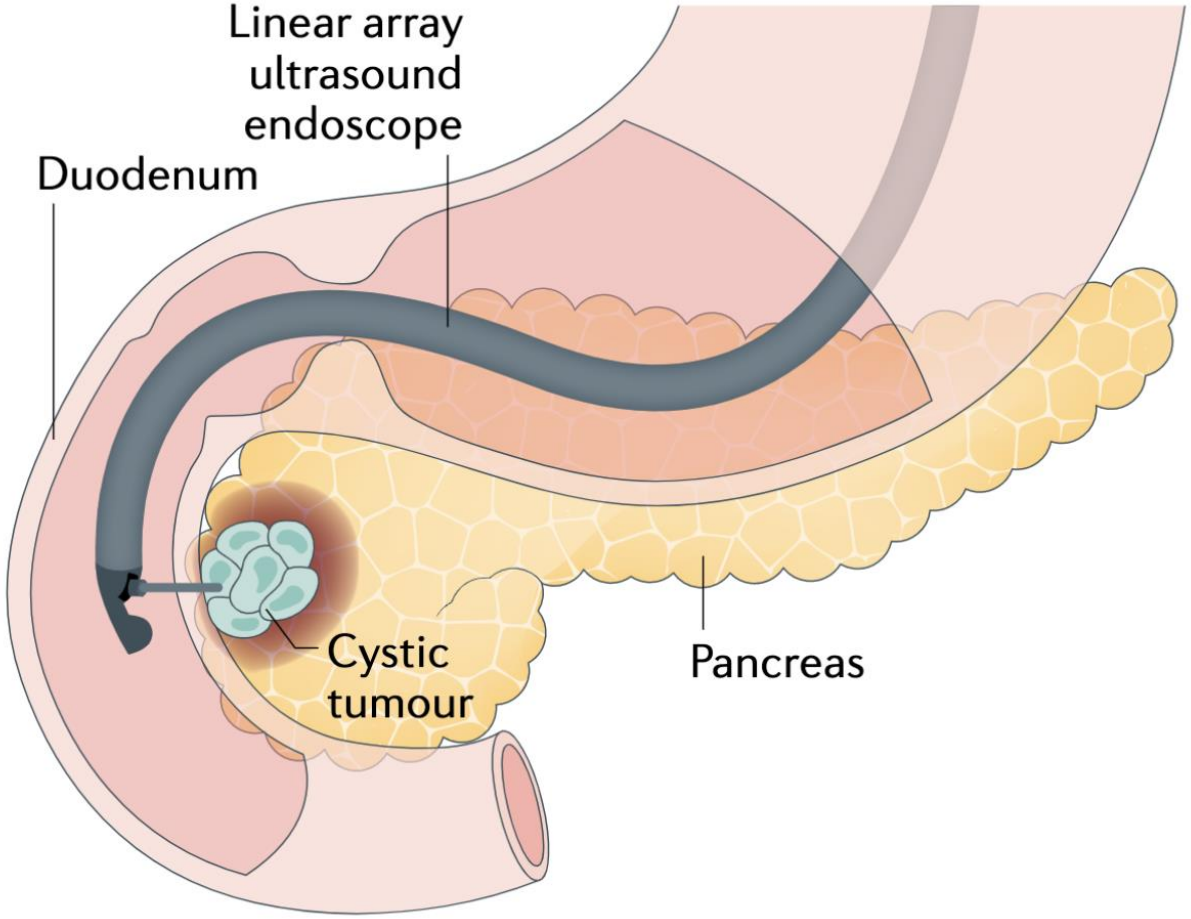
DNAJB1 – PRKACA fusions: also seen in fibrolamellar hepatocellular carcinoma

PDAC is molecular heterogenic

Small amounts of targetable driver-mutations

- Microsatellite instability (immunotherapy)
- ERBB2 amplifications (trastuzumab)
- Targets for Kinase Inhibitors (BRAF, FGFR2, FGFR3,…)
- Homologous Repair Deficiency (BRCA2, ATM,…)

Application: cyst fluid analysis



Diagnosis of cysts:

- Enzymes (CEA and amylase)
- Driver mutation analysis

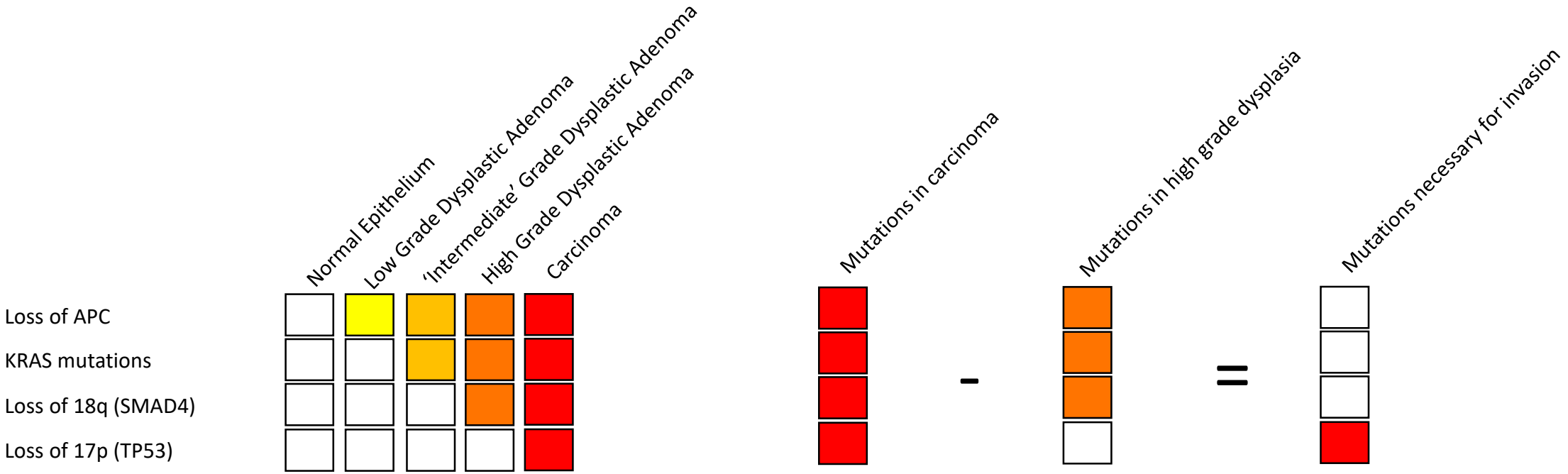
Risk stratification of IPMNs / MCNs:

- TP53, SMAD4: invasion

Singhi AD, Wood LD. Early detection of pancreatic cancer using DNA-based molecular approaches. Nat Rev Gastroenterol Hepatol. 2021

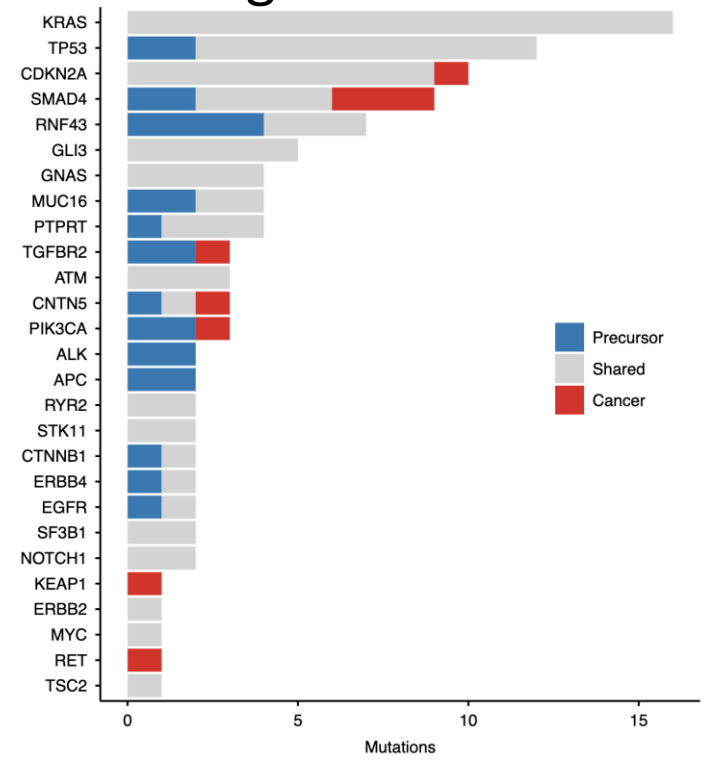
Discovering the driver mutations for invasion

- Vogelstein et al., New England Journal of Medicine, 1988:
  - FAP patients
  - Try to detect the previously discovered molecular aberrations of colorectal cancers in adenomatous polyps



IPMN to PDAC: driving invasion

- Deciphering the pathogenesis (whole-exome sequencing):
  - 4/18 cases had cancer specific SMAD4/TGFBR2 mutations
  - Other cancer-specific driver-genes were CDKN2A, CNTN5, PIK3CA, KEAP1 and RET



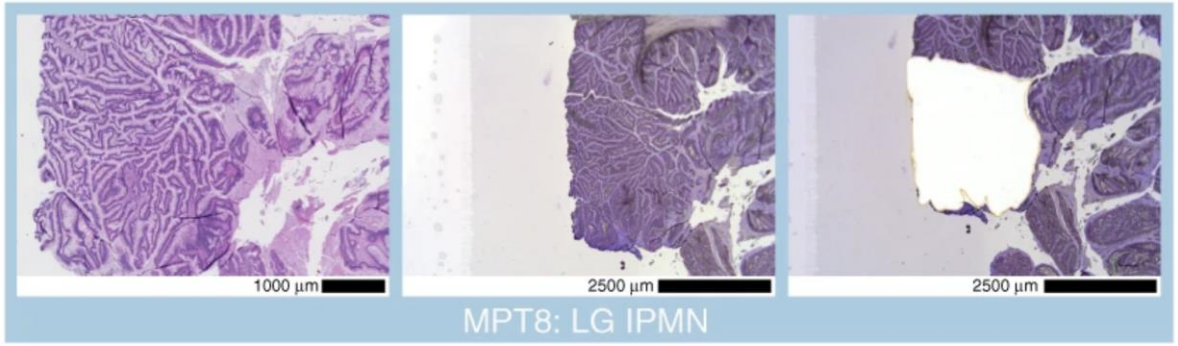
Noë M. et al. Genomic characterization of malignant progression in neoplastic pancreatic cysts. Nat Commun. 2020

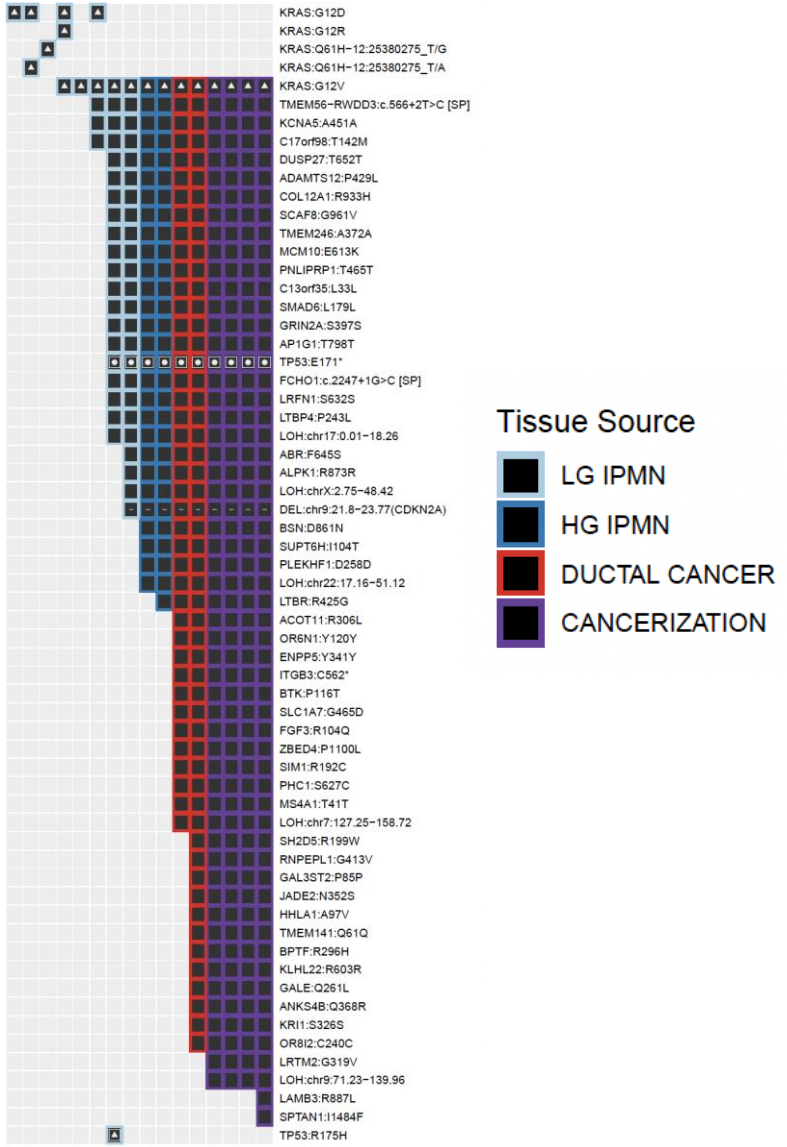
Association, but not always causation

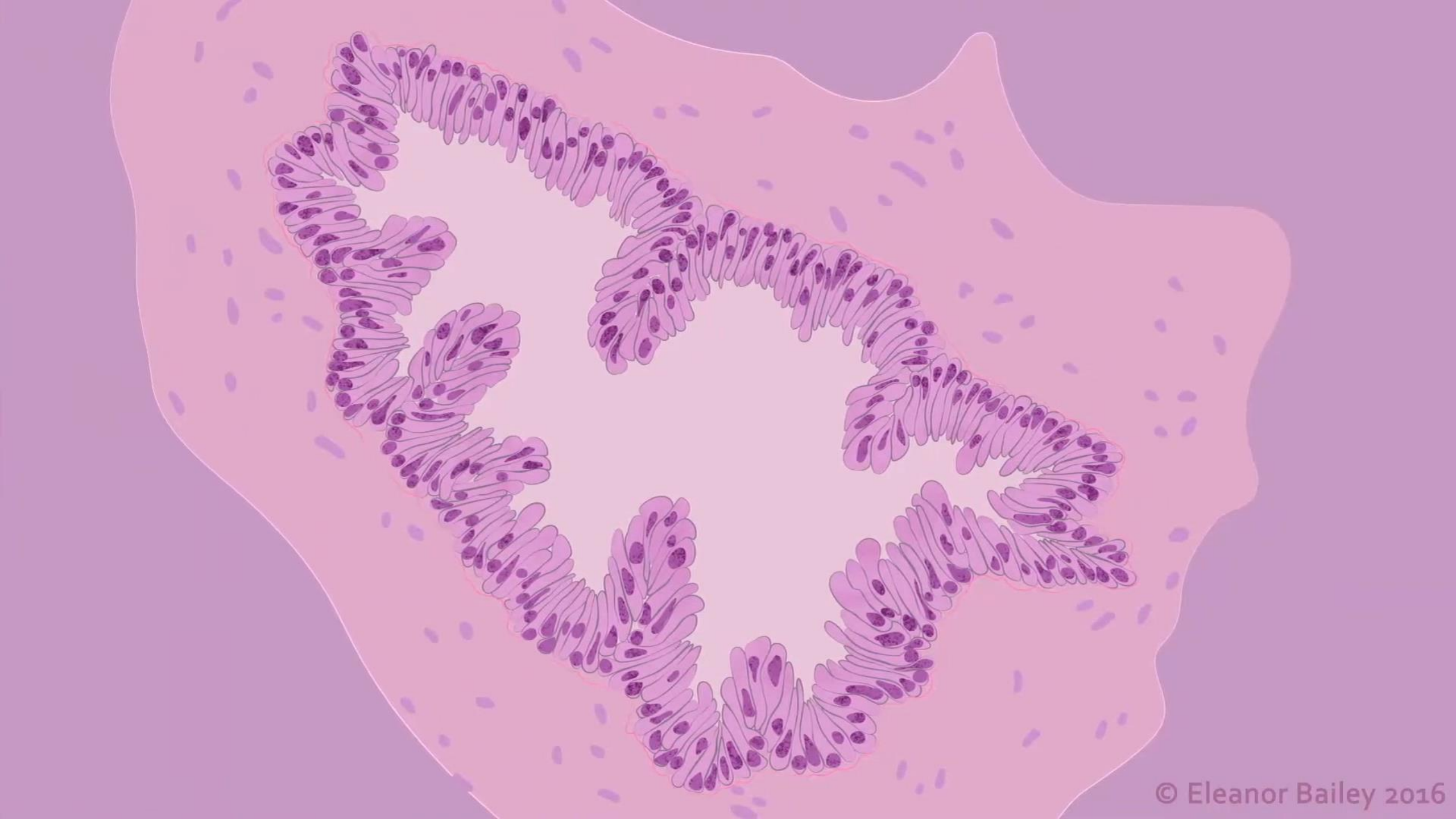
- Clonal relationship between concurrent IPMN and PDAC:
  - 1/3 of IPMNs in patients with a PDAC is not clonally related!
    - Different driver mutations
  - Probably a smaller PanIN lesion resulted in the PDAC
  - Reporting:
    - Just describe what you see (IPMN, PanIN and PDAC)
    - Use of ‘Malignant IPMN’ is discouraged

Felsenstein M, Noë M et al. IPMNs with co-occurring invasive cancers: neighbours but not always relatives. Gut. 2018

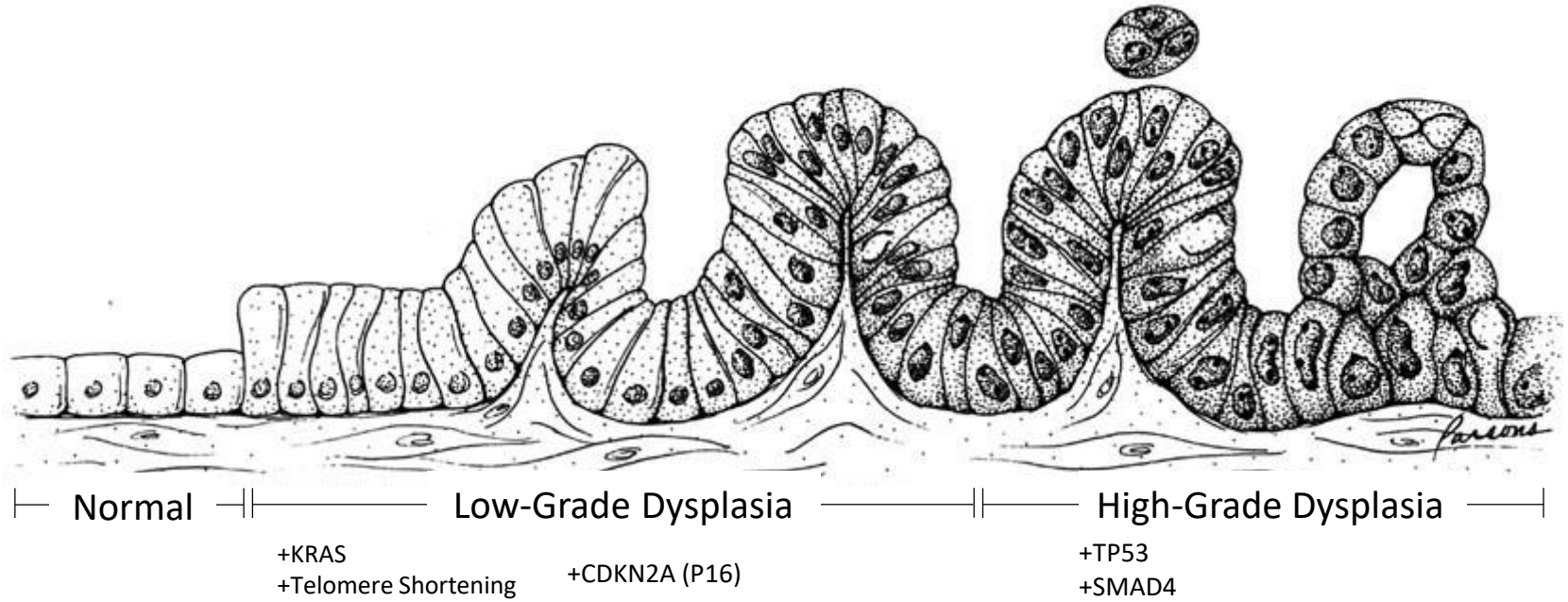
Cancerization: molecular evidence







Implications of the Driver Mutations Sequence



- The sequence is important to evaluate risk from germline mutations
  - CDKN2A (P16): early driver mutation in PDAC
    - Germline mutations: Familial Atypical Multiple Mole Melanoma syndrome (FAMMM) have high risk for PDAC
  - SMAD4: late driver mutation in PDAC
    - Germline mutations: Juvenile Polyposis syndrome have normal / low risk for PDAC

Conclusions

- KRAS is targetable
- Small amount of PDACs harbour targetable driver mutations
- PDAC is heterogeneous and subgroups have different prognosis
  - Precursors have different mutations, which can be used for diagnosis on cyst fluid
  - Small amount of PDACs have targetable driver mutations
- Co-occurring IPMNs and PDACs are not always related
- PDACs can grow back in ducts and present as ‘precursor’ lesion

Thank you

Prof. Dr. Ralph Hruban
Prof. Dr. Victor Velculescu
Prof. Dr. Offerhaus
Prof. Dr. Scott Kern
Prof. Dr. Anne Hoorens
Dr. Laura Wood
Dr. Lodewijk Brosens