



ORDINE  
MEDICI CHIRURGHI  
E ODONTOIATRI  
DELLA PROVINCIA  
DI BRESCIA

COMMISSIONE CULTURA  
Coordinatore: Dott. Germano Bettoncelli

*In collaborazione con*



Fondazione  
Nadia Valsecchi

*Convegno*

## **DIAGNOSI E CURA DEI TUMORI PANCREATICI**

*Sala Conferenze Ordine Medici ed Odontoiatri - Via Lamarmora n. 167 (Palazzo il Diamante) - Brescia*

**19 maggio 2018 - ore 8.00**

## **MOLECULAR PATHOLOGY OF PDAC**

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Università di Verona



NATIONAL  
CANCER  
INSTITUTE

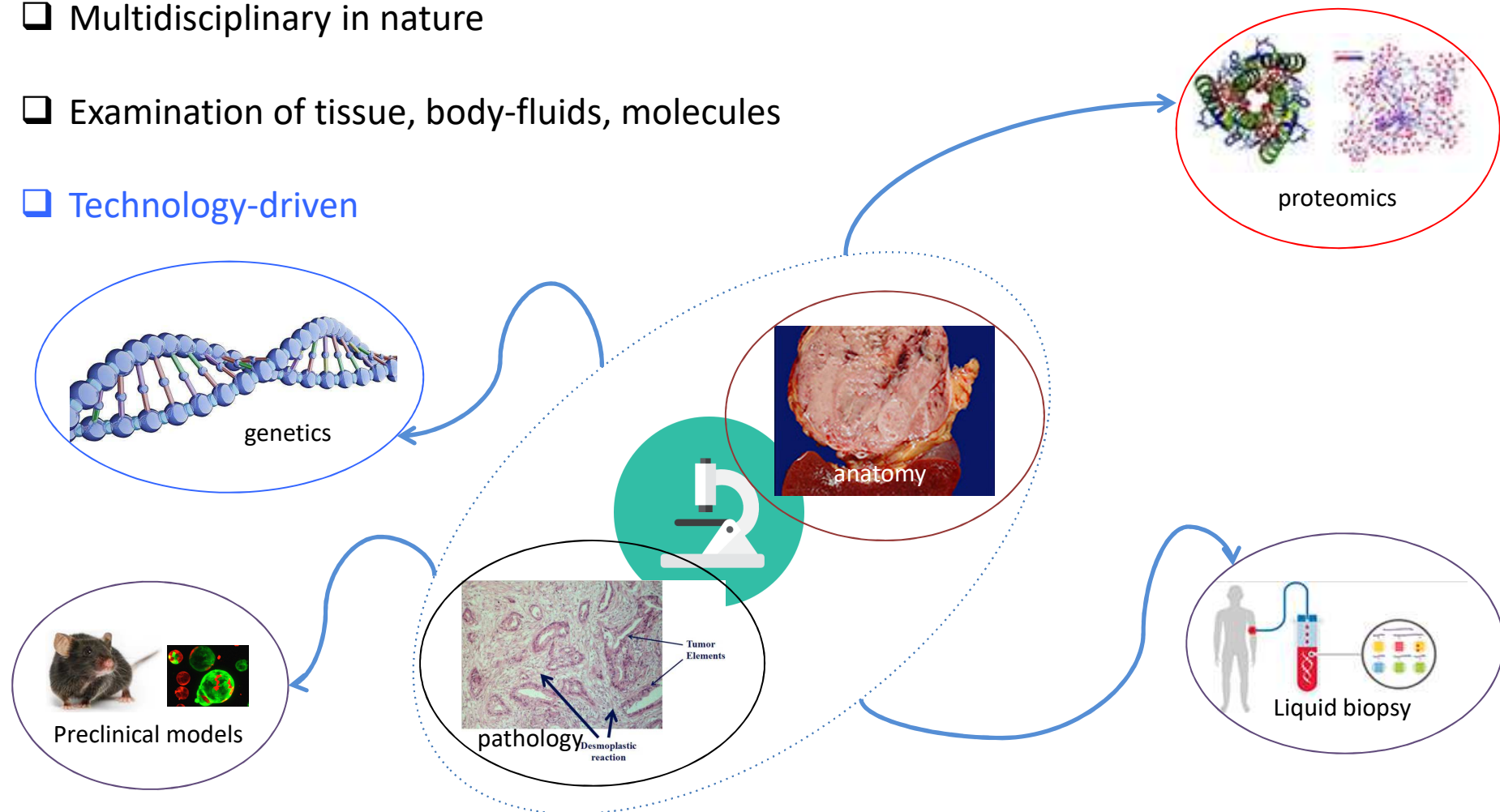


Fondazione  
Nadia Valsecchi

# MOLECULAR PATHOLOGY

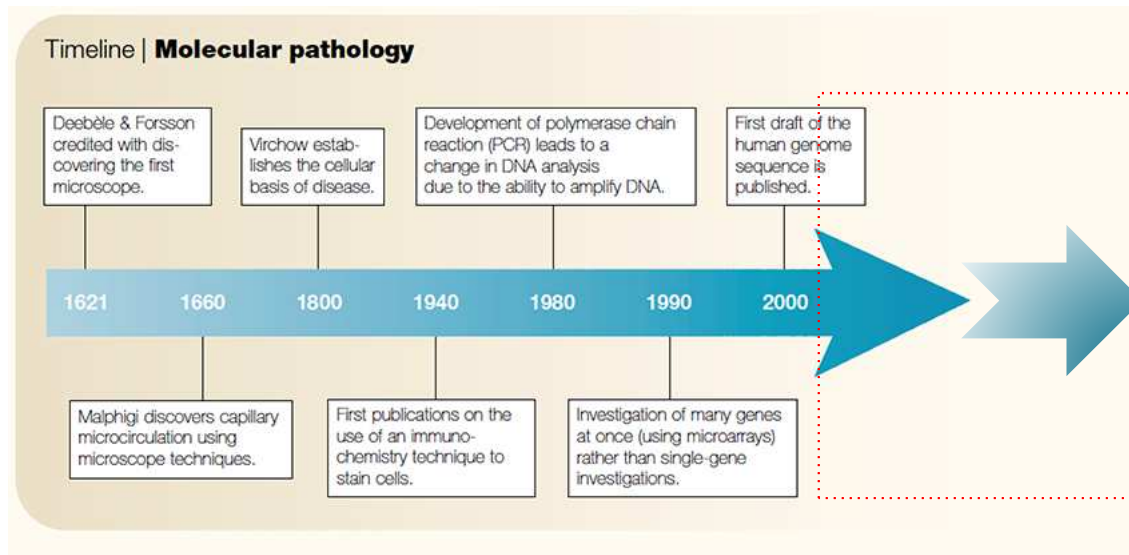
**Molecular Pathology** is an emerging discipline (WIKIPEDIA)

- ❑ A crossover discipline (anatomy, clinical pathology, biochemistry, genetics, proteomics)
- ❑ Multidisciplinary in nature
- ❑ Examination of tissue, body-fluids, molecules
- ❑ Technology-driven

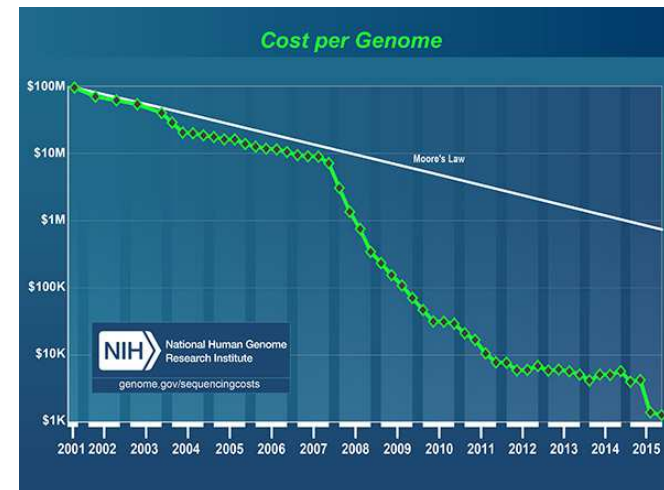


# MOLECULAR PATHOLOGY

Incredibly fast evolution in recent years



Lakhani & Ashworth 2001. Nature



# MOLECULAR PATHOLOGY: THE VISION

## Box 1 | The future of personalized medicine

The year is 2020. I wake up and feel the lump under my arm that has been bothering me for several weeks. I decide to make an appointment with the doctor to find the cause, especially since my personal genetic analysis has highlighted alleles that are associated with an increased risk of cancer.

The doctor's receptionist views my electronic health record online before I am buzzed in to see the doctor. Once I have explained the problem, a biopsy from the offending lymph-node is taken, the tissue is flash-frozen using the nitrogen quick-freeze system, and then delivered to the laboratory downstairs for a rapid molecular work-up.

DNA from the tissue is sequenced to identify any mutations in the 500 most-common genes known to be involved in cancer. Tissue sections are analyzed using high-resolution fluorescent optical images. A blood sample is also taken to check my background genomic DNA sequence, concentrating on alleles known to predispose to lymphoma. Sequences for the genes encoding drug-metabolizing enzymes and drug-distribution proteins are also obtained.

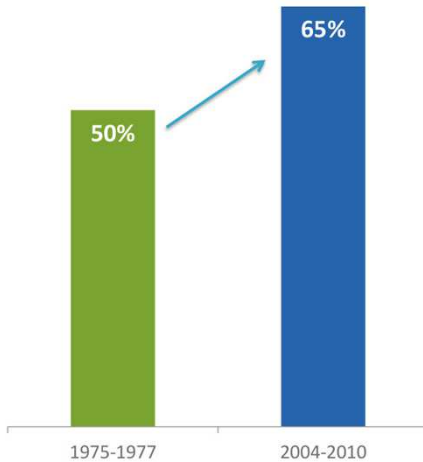
A proteomic work-up is undertaken to look at protein profiles and post-translational modifications. I also undergo new-generation imaging so the gross pathology of my organs can be viewed in three-dimensions. Two hours later, I review the results on my handheld computer device. The results have been predigested and presented as a simple digital read-out so that a diagnosis, prognosis and appropriate treatment can be derived.

Fortunately, the overall molecular and cellular pathology of the lymph-node is considered normal. Apart from my pre-existing heart disease, all other organs appear to be healthy and I am prescribed an anti-inflammatory drug.

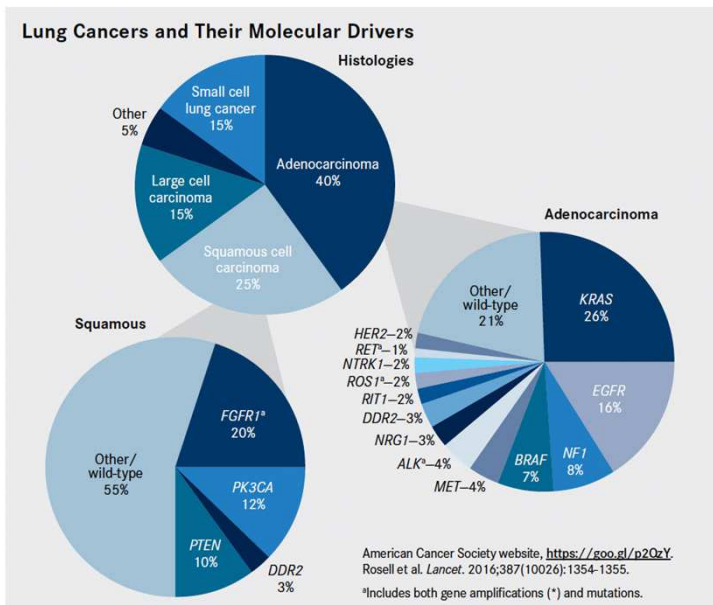
I leave the doctor's office with a sigh of relief that all appears to be well.

# MOLECULAR PATHOLOGY: ARE WE GETTING THERE?

5-Year Survival Rates for Colorectal Cancer Patients

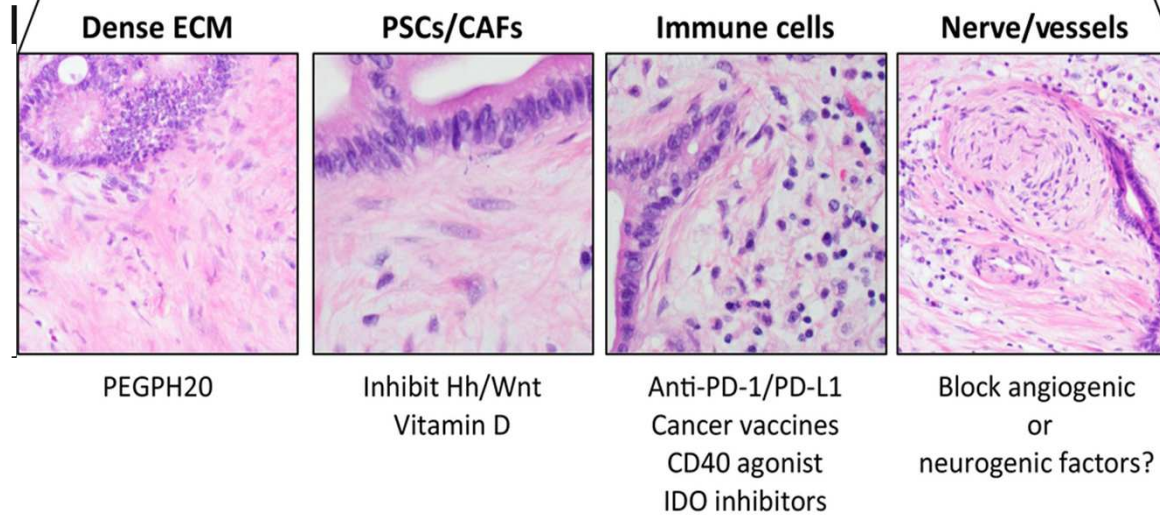
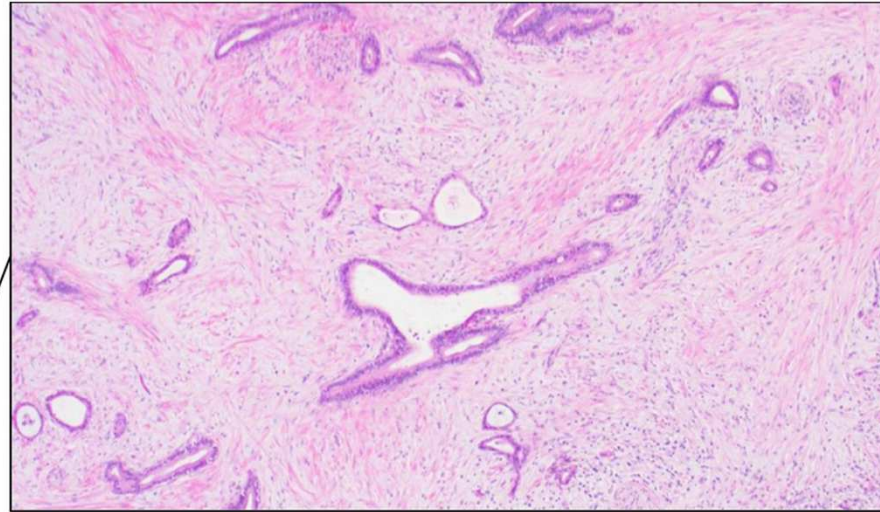


- ◆ Identification of EGFR monoclonal antibodies
- ◆ Identification of KRAS mutations as predictive biomarker
- ◆ MSI tumors responders to Immunotherapy

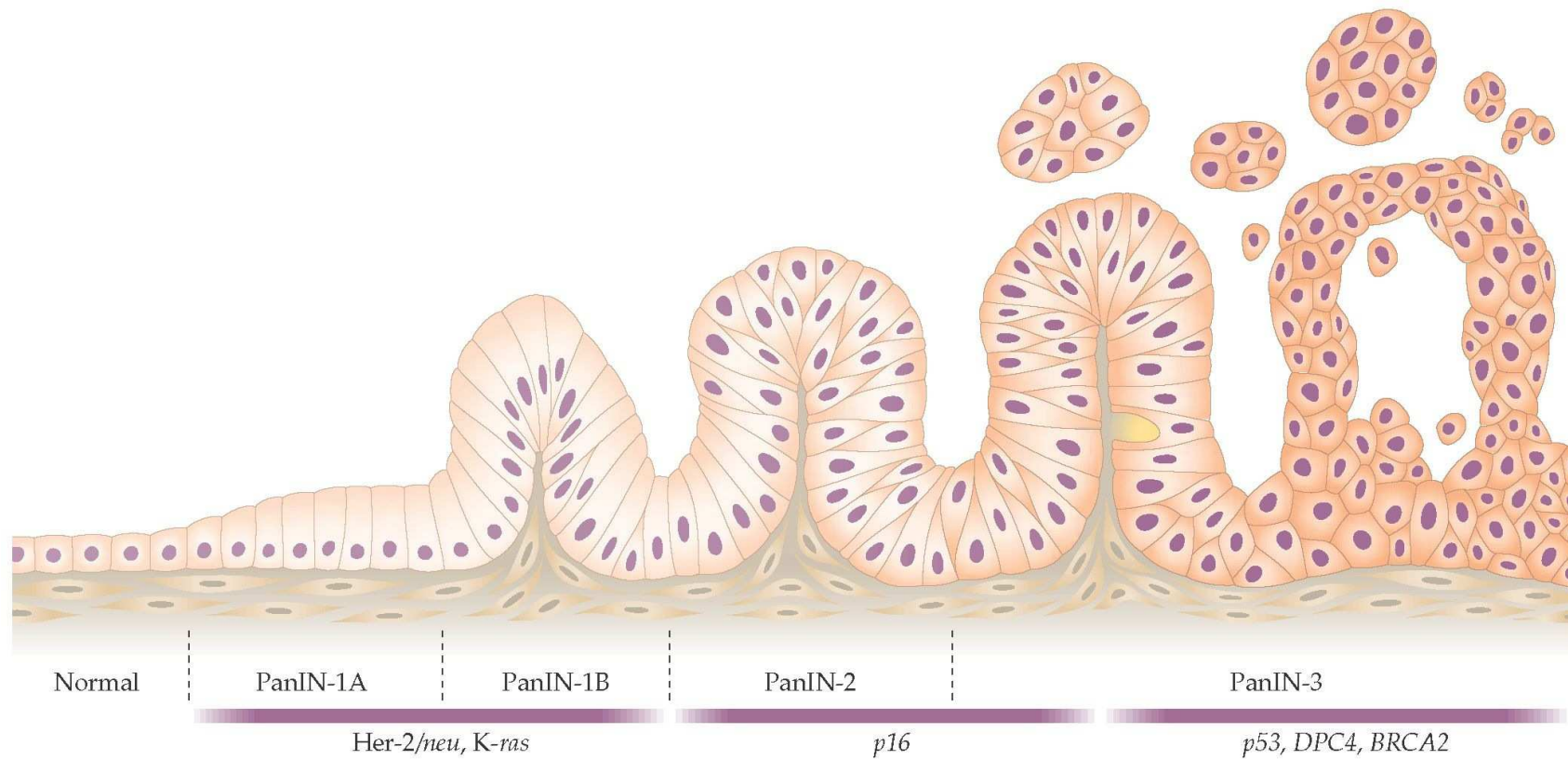


- ◆ Identification of EGFR mutations
- ◆ Identification of fusion genes
- ◆ Opportunity for immunotherapy

# WHY IT IS SO COMPLEX

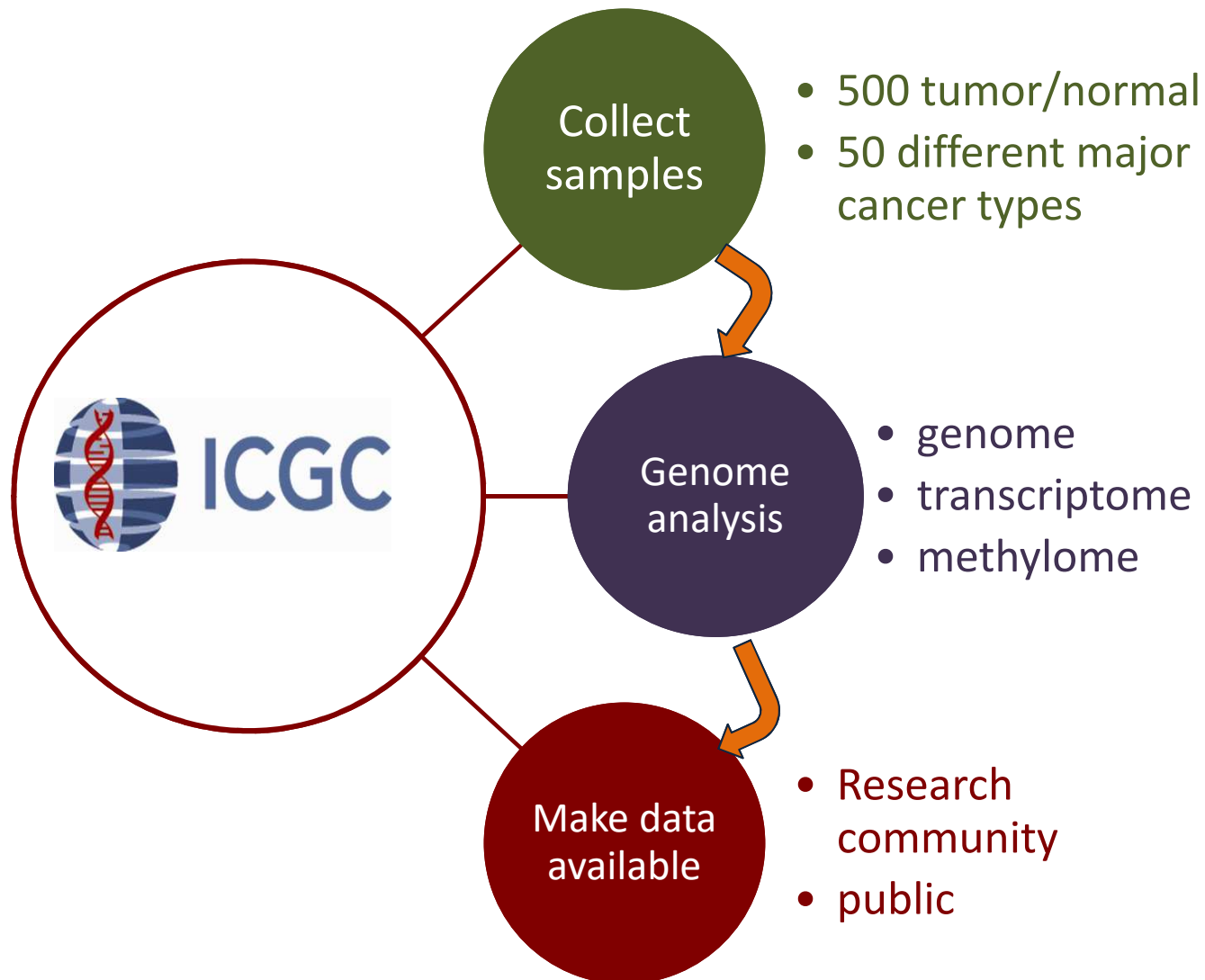


# What we have been doing in the past



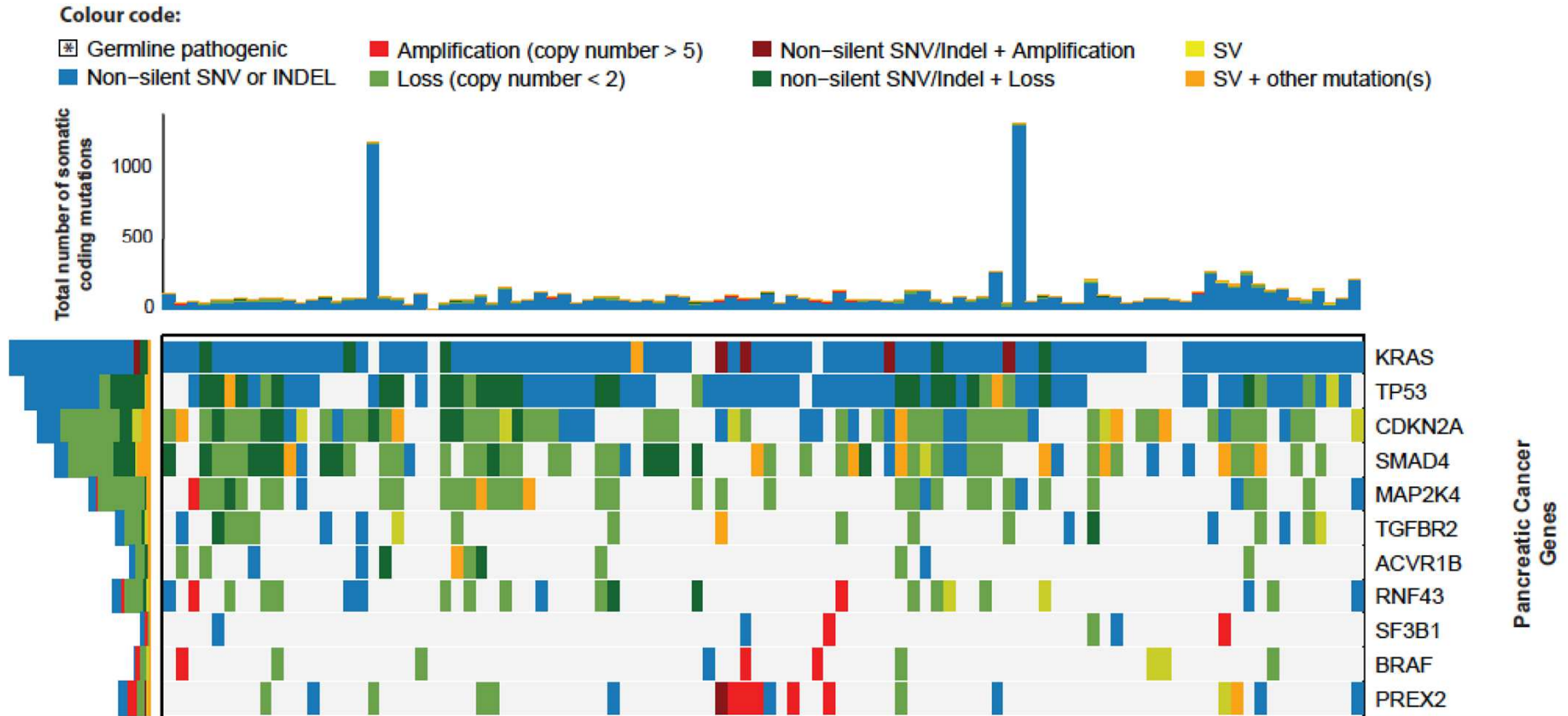
# MOLECULAR PATHOLOGY: WHAT WE HAVE DONE

## MULTIDIMENSIONAL TUMOR PROFILING



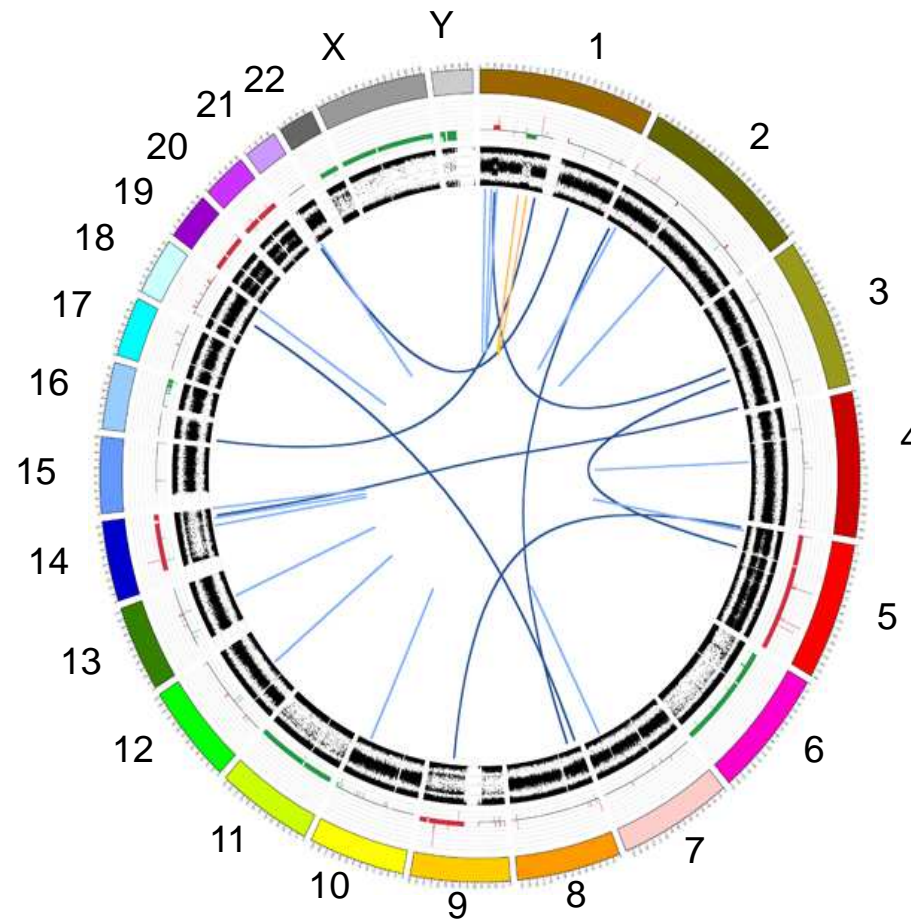


# WGS redefines the molecular landscape of PDAC



Nearly universal features of PDAC:  
activation of KRAS and inactivation of TP53

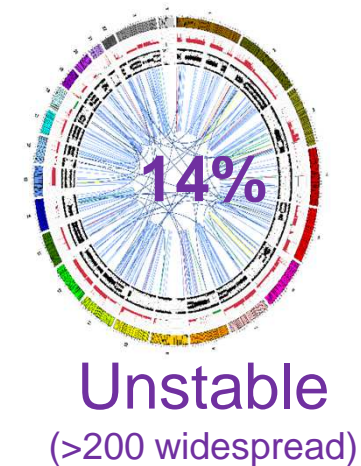
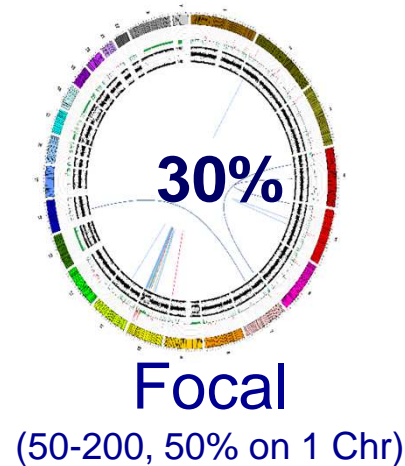
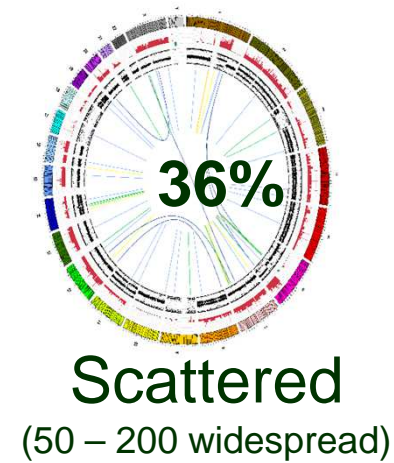
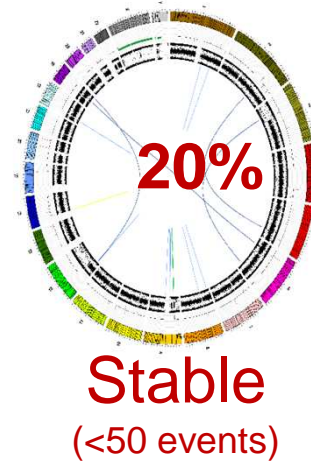
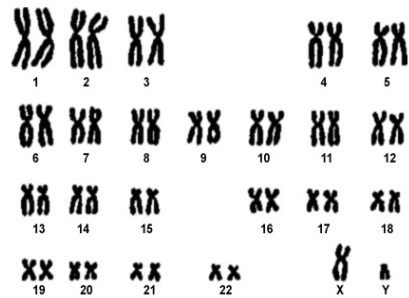
# WGS redefines the molecular landscape of PDAC



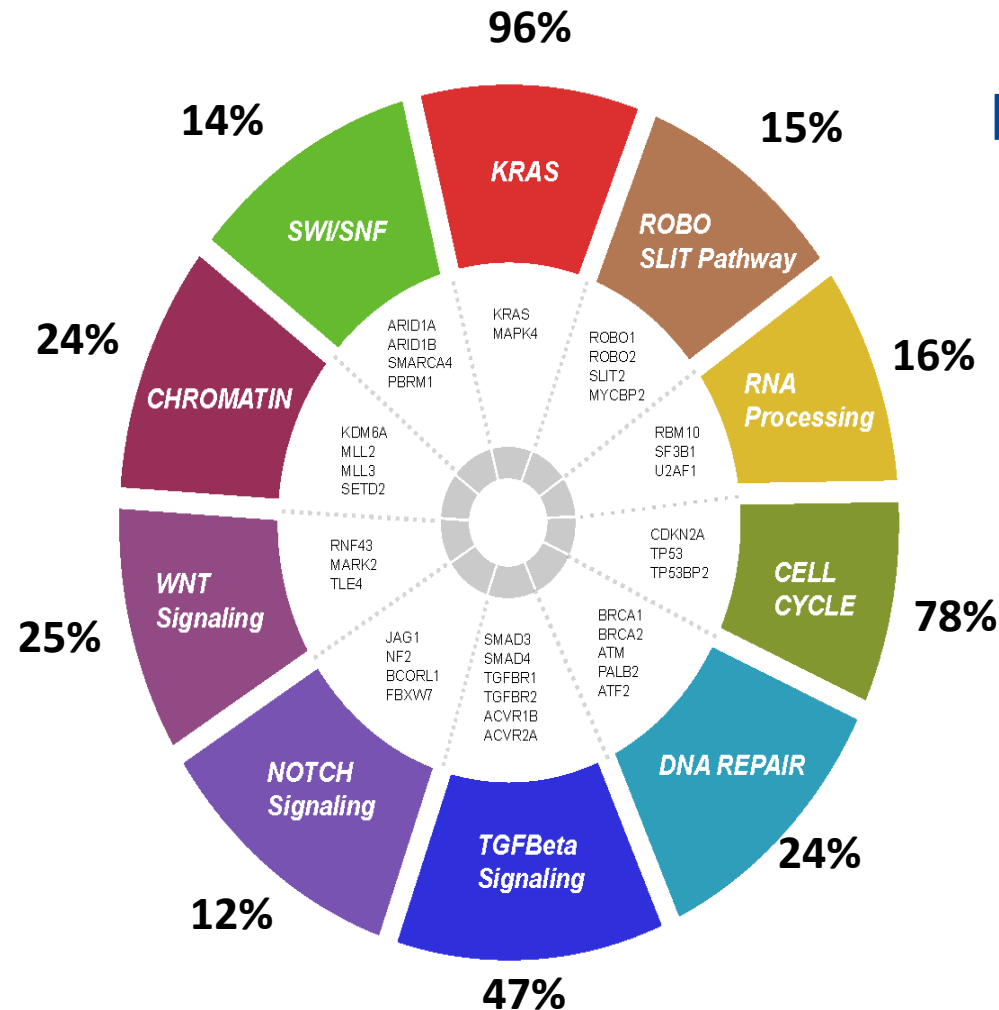
- |   |  |  |   |
|---|--|--|---|
|  Intra chromosomal rearrangement |  Duplication        |  Inversion          |  Amplified inversion |
|  Inter chromosomal translocation |  Tandem duplication |  Foldback inversion |  Deletion            |

# WGS identifies 4 subtypes of PDAC

## WGS-KARYOTYPE



# WGS identifies the molecular landscape of PDAC

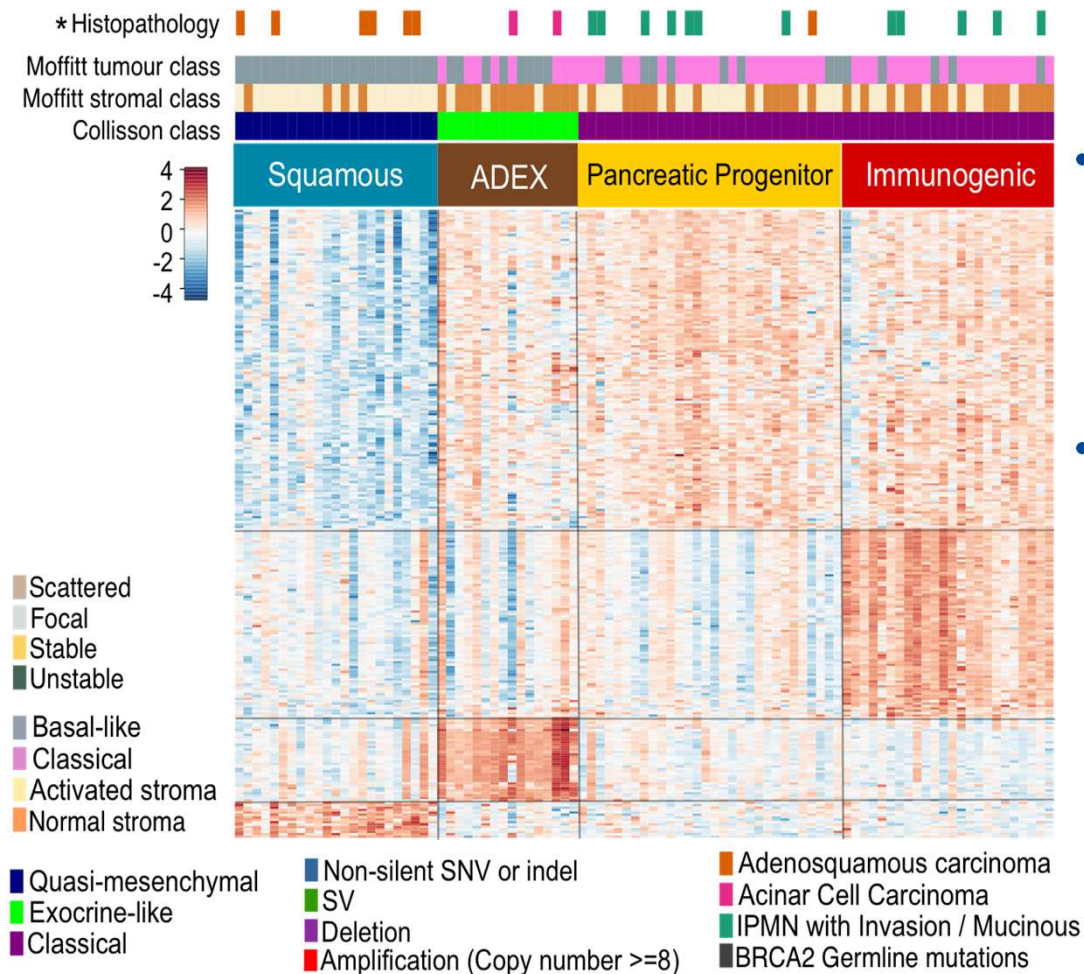


## Driver Gene Analysis (N = 456)

- 10 pathways
- 32 recurrently mutated genes

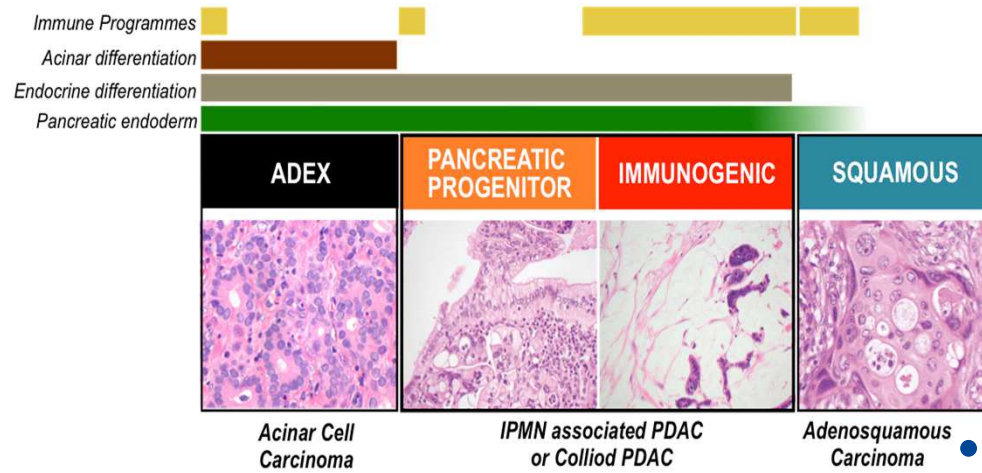
# RNAseq identifies 4 functional subtypes of PDAC

## RNAseq of 96 cases

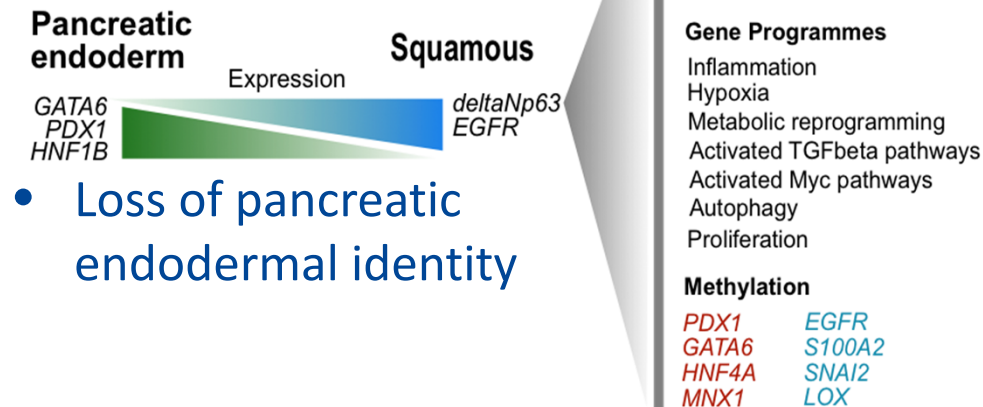


- 4 classes based on transcription factors and downstream targets
- Enriched with specific histological features

# RNAseq identifies 4 functional subtypes of PDAC

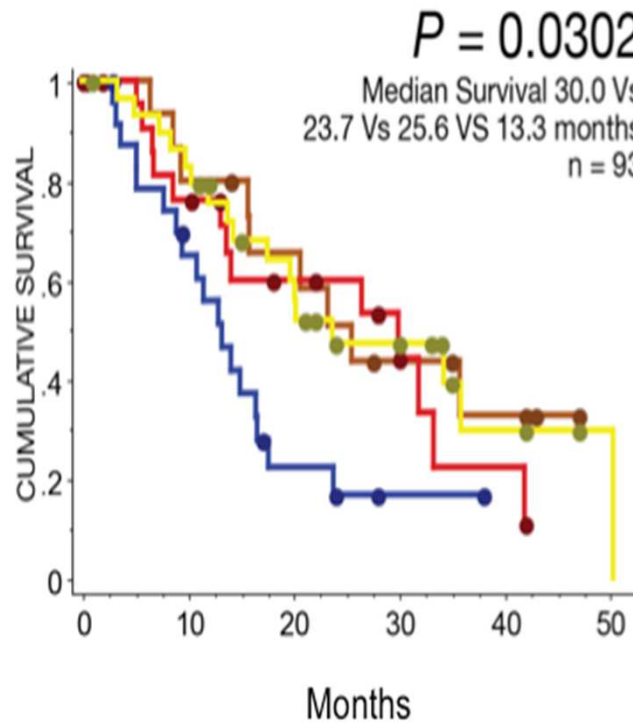


• Enriched for *TP53* and *KDM6A* mutations



• Loss of pancreatic endodermal identity

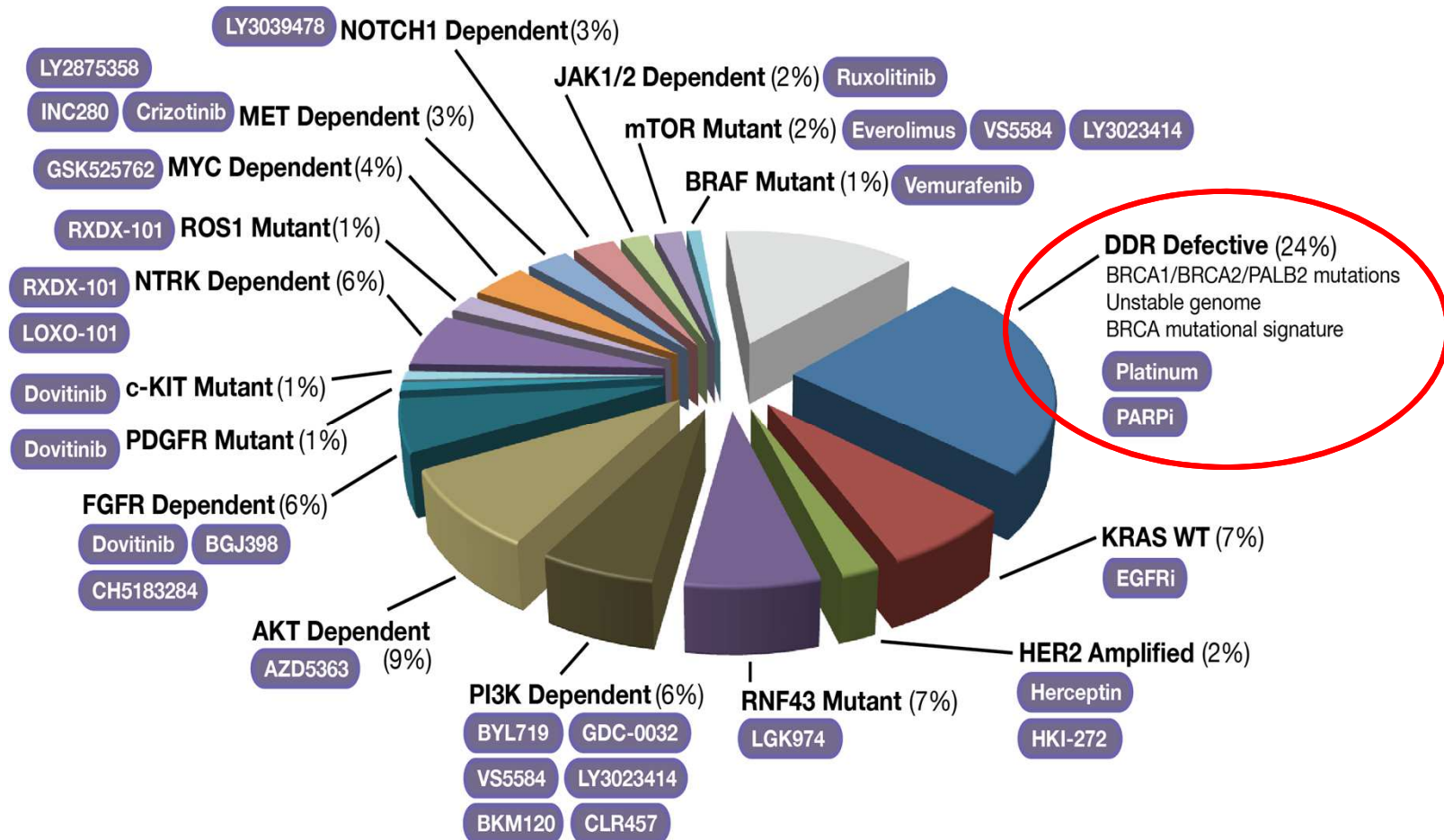
# RNAseq identifies 4 functional subtypes of PDAC



- Squamous subtype has the worst prognosis
- Distinct responses to therapy
- Distinct immune contexture

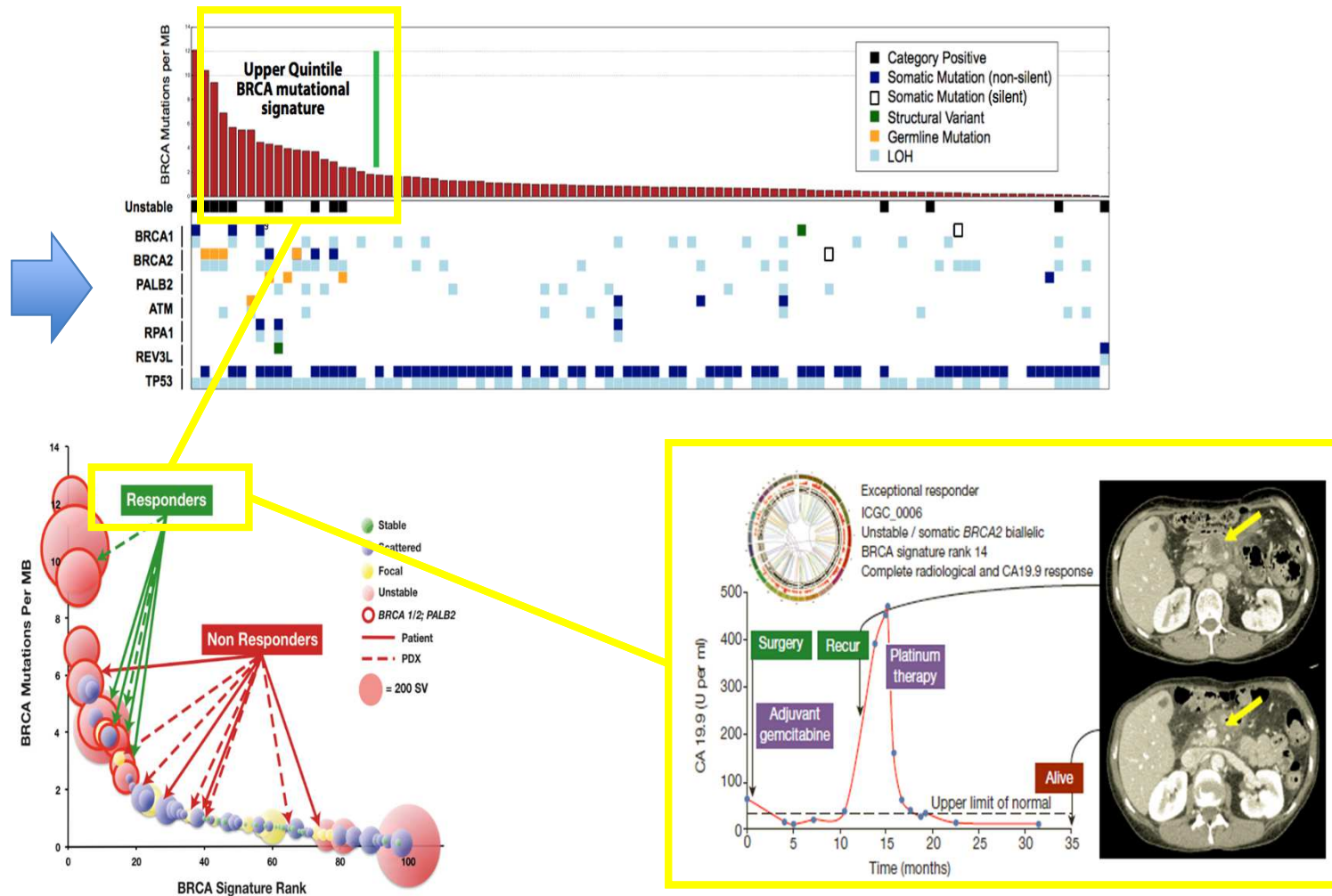
# The actionable genome: room for testing-repurposing

## Pancreatic Cancer “Actionable Genome”



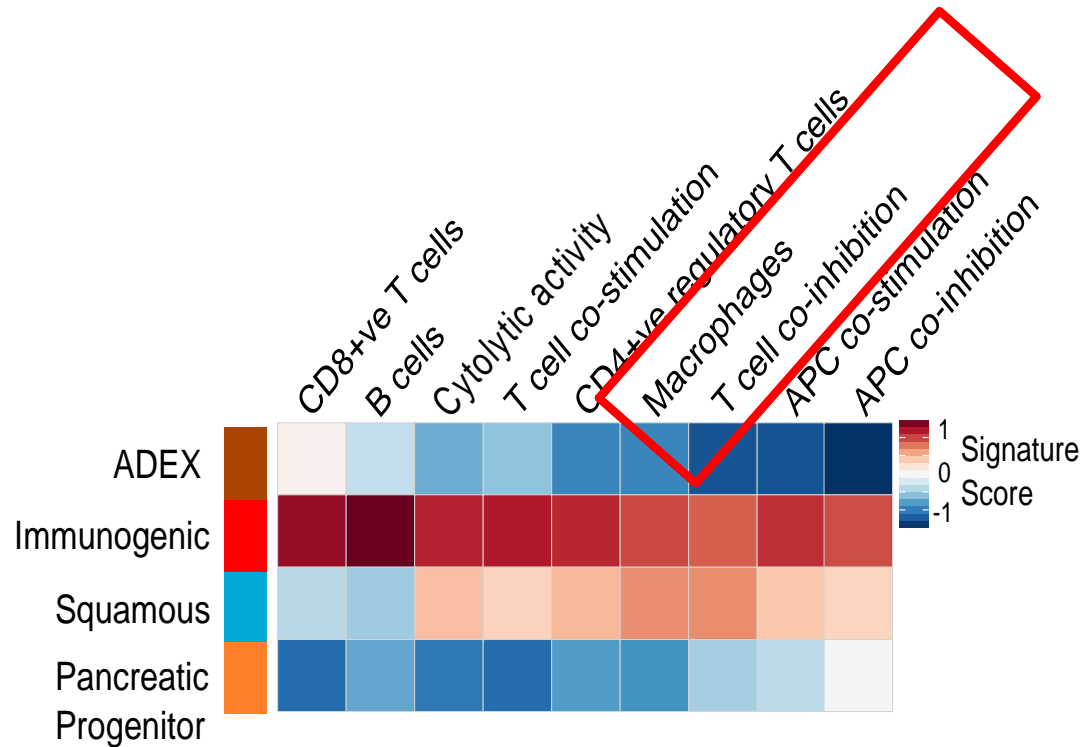


# The actionable genome: examples of effectiveness

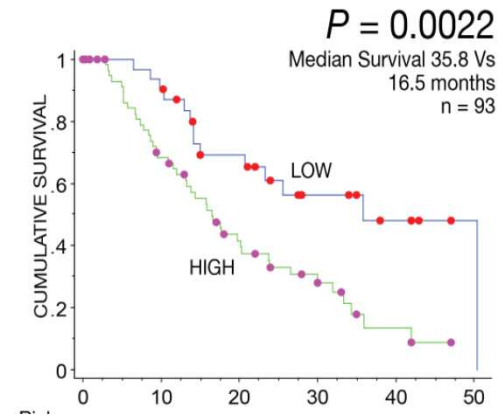


# RNAseq identifies 4 functional subtypes of PDAC

## Immunogenic Subtype



### MACROPHAGE SIGNATURE



### T CELL CO-INHIBITION SIGNATURE

