Biobanking: An Investment in Cancer Public Health

Rita T. Lawlor

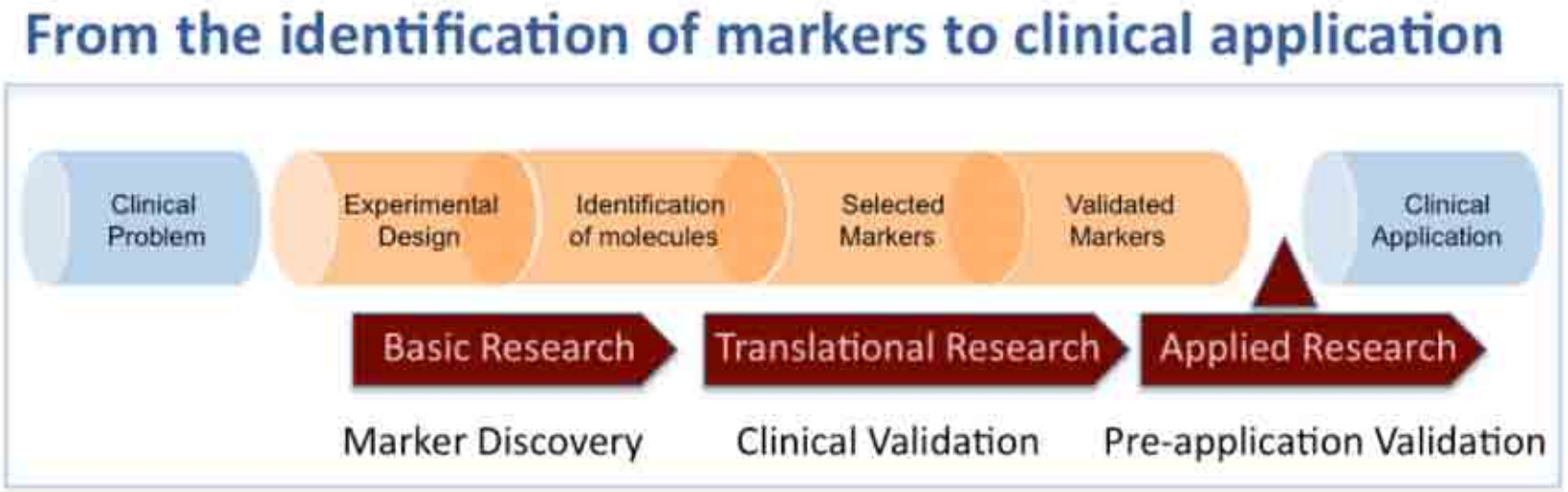
ISBER Regional Director
International Society for Biological and Environmental Biorepositories

Biobank Manager
Applied Research on Cancer Centre
University of Verona, Italy

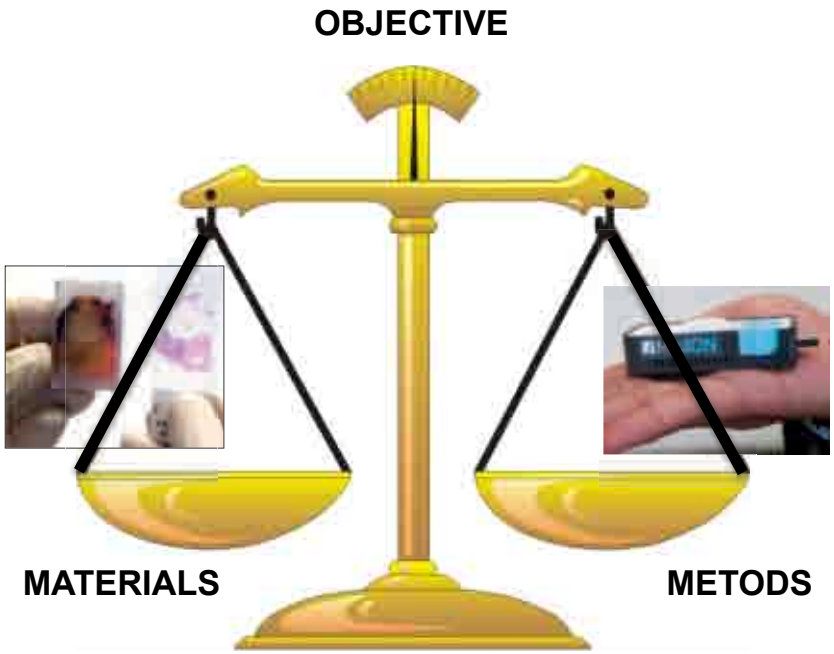
CLINICAL PRACTICE

1. Diagnosis
2. Prognosis
3. Predict drug efficacy
4. Follow up

Biobanks help in the fight against deadly diseases such as cancer

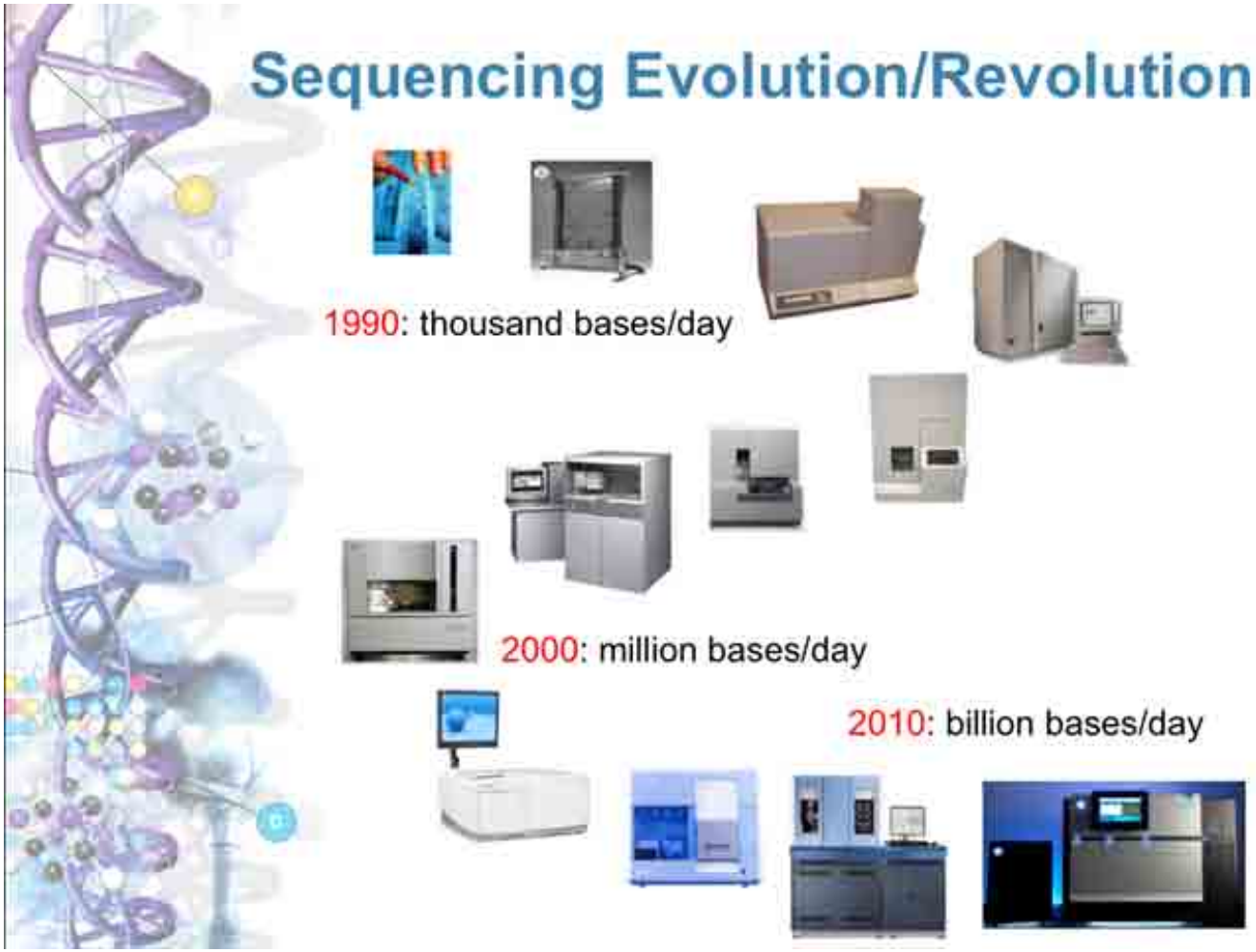


Understand Biological Precision



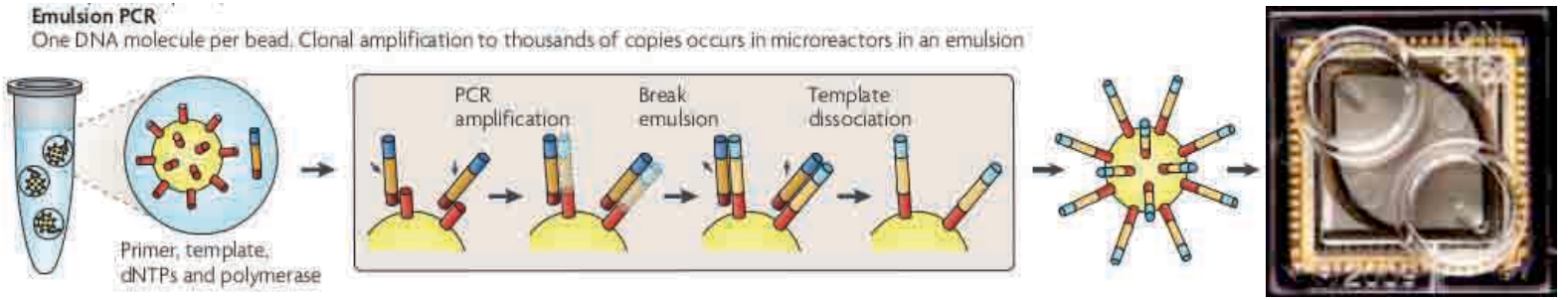

High Quality, Ethically-Collected Specimens
are Critical Research Tools
It cannot be a local process
Requires international collaboration
Collaboration across disciplines
Complementary knowledge to be integrated
Bring together science and policy makers

Whole Genome Sequencing

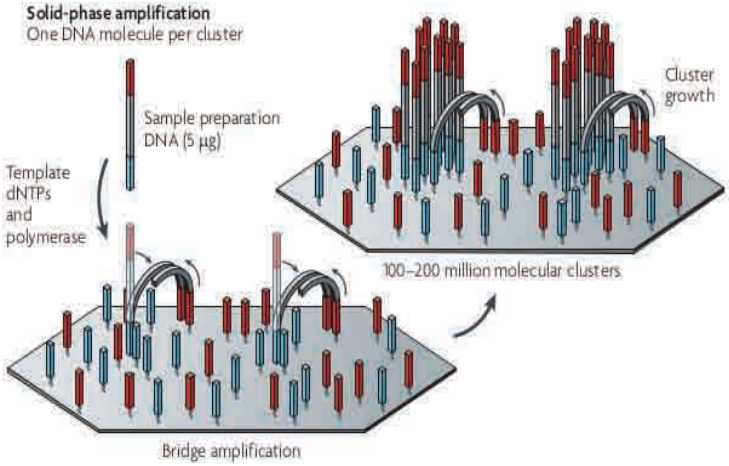


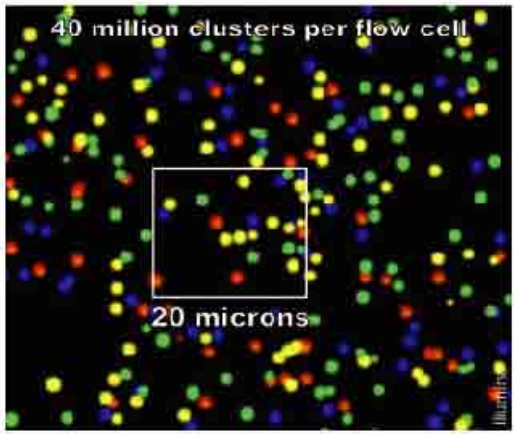
Next-Gen sequencing

A. Ion Torrent



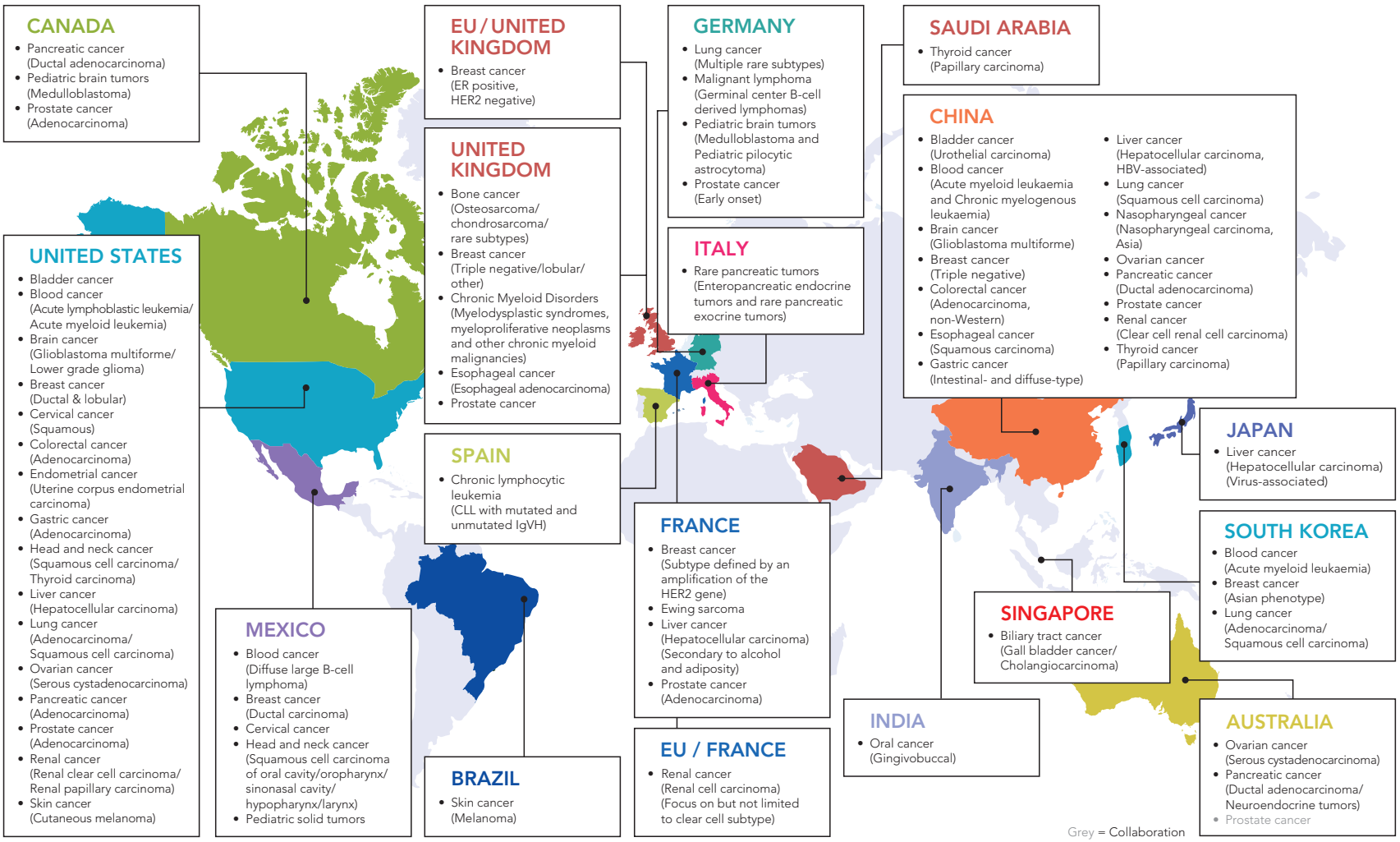
B. Illumina



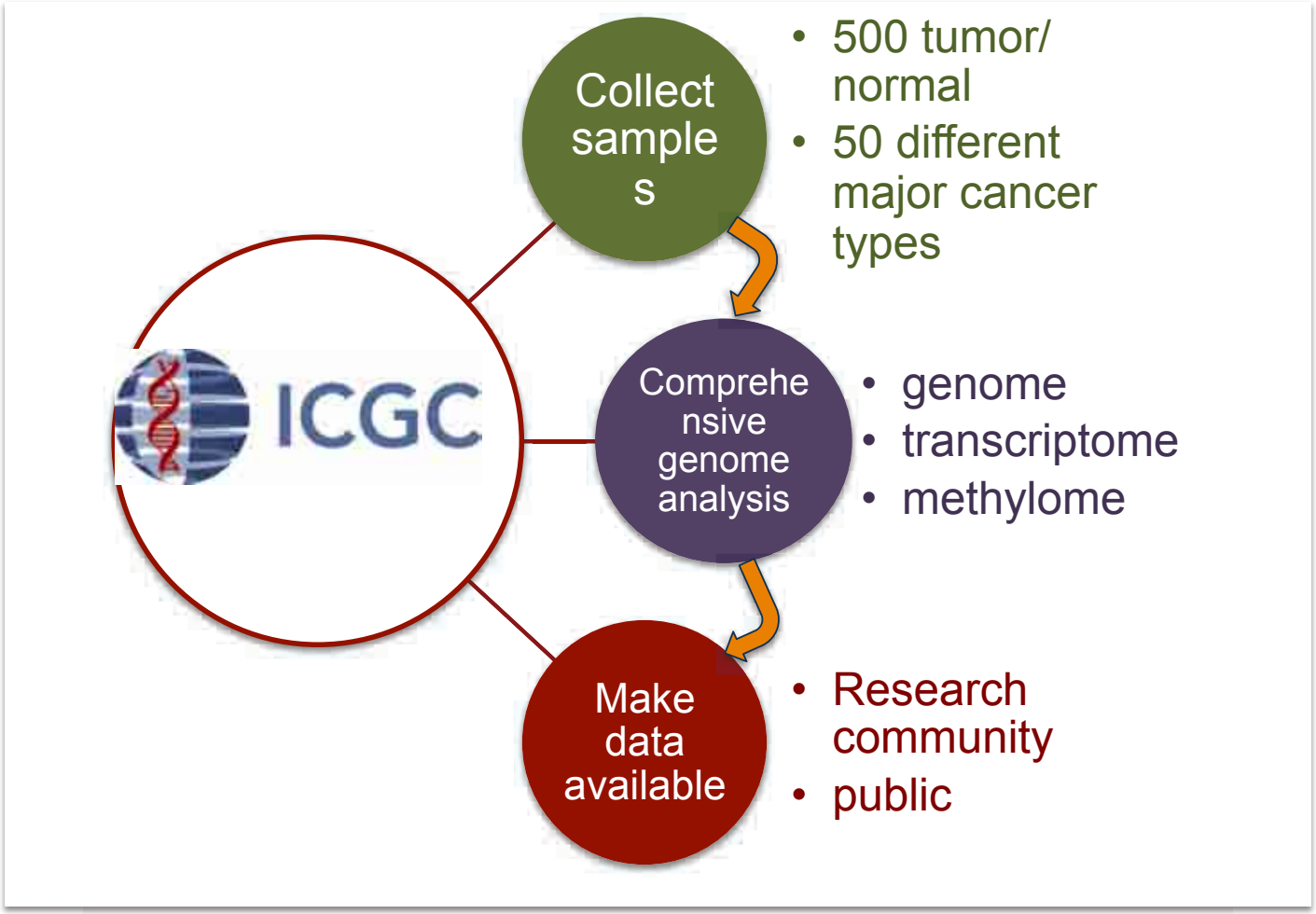


Metzker, *Nat Rev Genetics* (2010 Jan; 11)

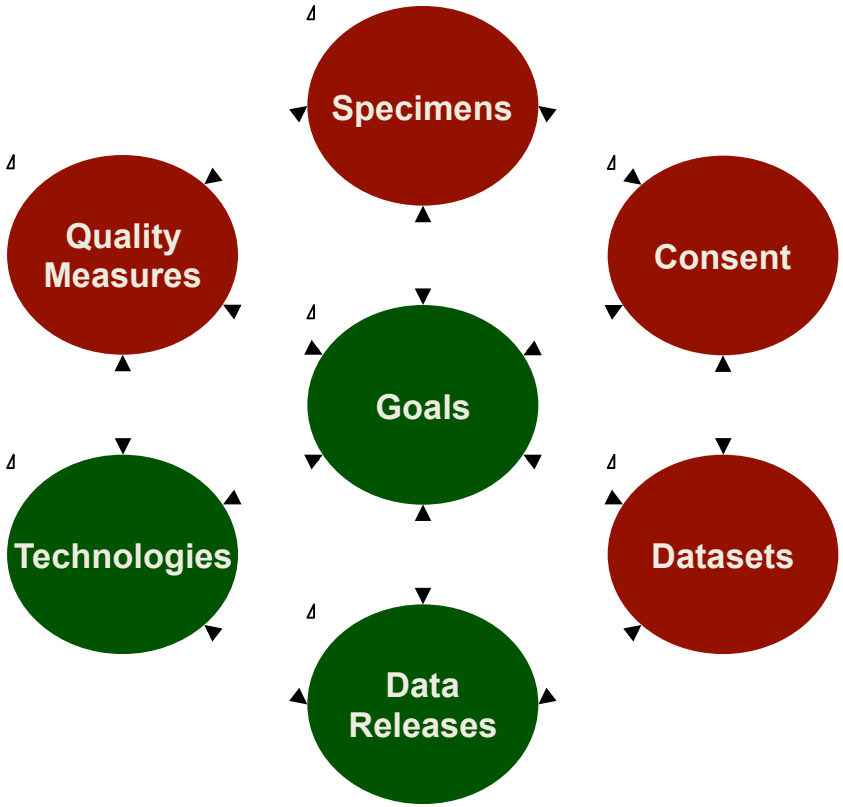
High Quality, Ethically-Collected Specimens are Critical Research Tools



High Quality, Ethically-Collected Specimens are Critical Research Tools

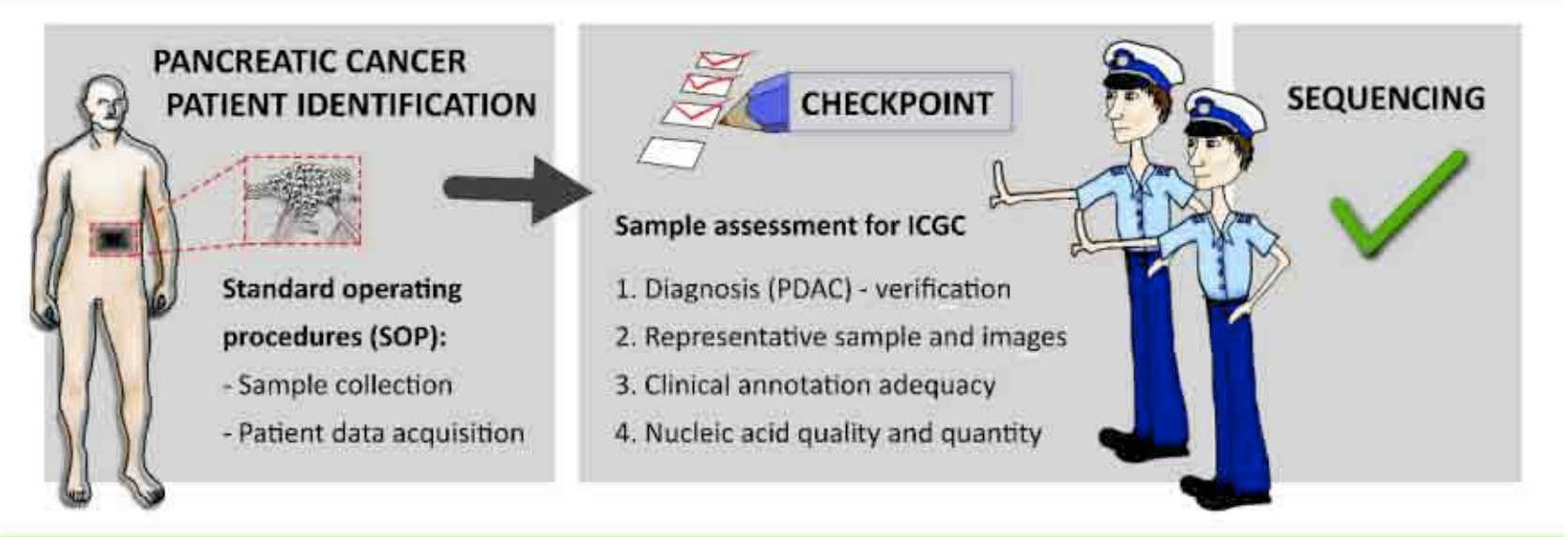


High Quality, Ethically-Collected Specimens are Critical Research Tools



Major issues addressed in ICGC consortium

High Quality, Ethically-Collected Specimens are Critical Research Tools



How do we define QUALITY?

A boy asks his father:

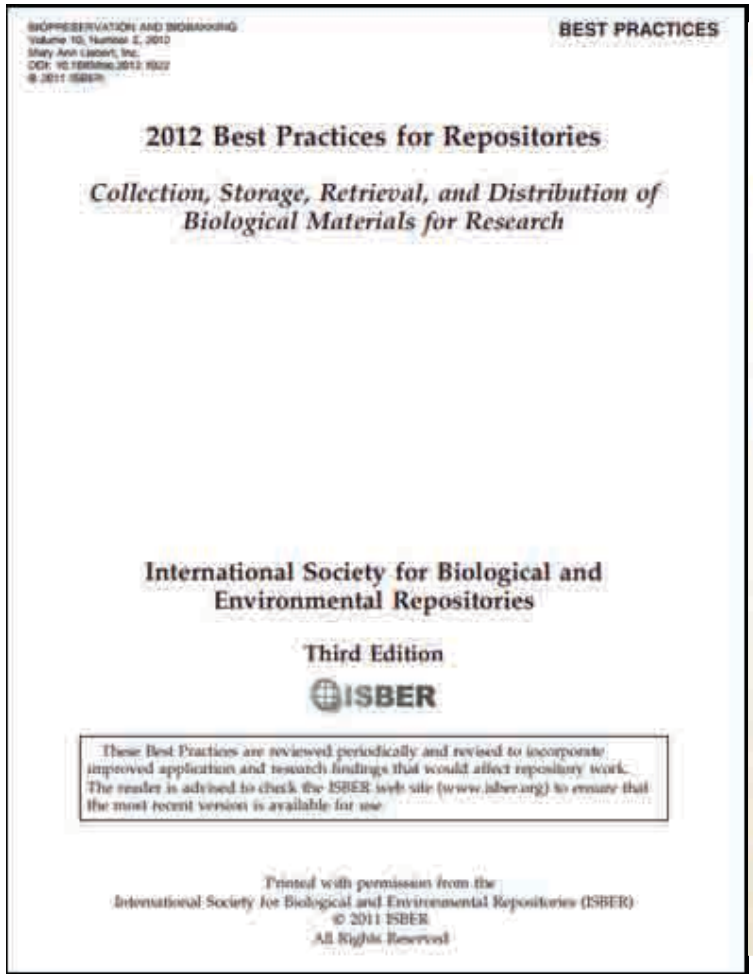
“Dad, a ferrari is a red car with a horse?”

“Yes, son why?”

“Baecause i think i just saw one”


Marlboro
vodafone
vodafone
AMD

ISBER Best Practices for Repositories



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BEST PRACTICES

2012 Best Practices for Repositories

Collection, Storage, Retrieval, and Distribution of Biological Materials for Research

International Society for Biological and Environmental Repositories

Third Edition

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These Best Practices are reviewed periodically and revised to incorporate improved application and research findings that would affect repository work. The reader is advised to check the ISBER web site (www.isber.org) to ensure that the most recent version is available for use.

Specimen Collection, Processing, Storage And Retrieval

Legal And Ethical Issues in Biobanking

Specimen Access, Distribution, Use And Destruction

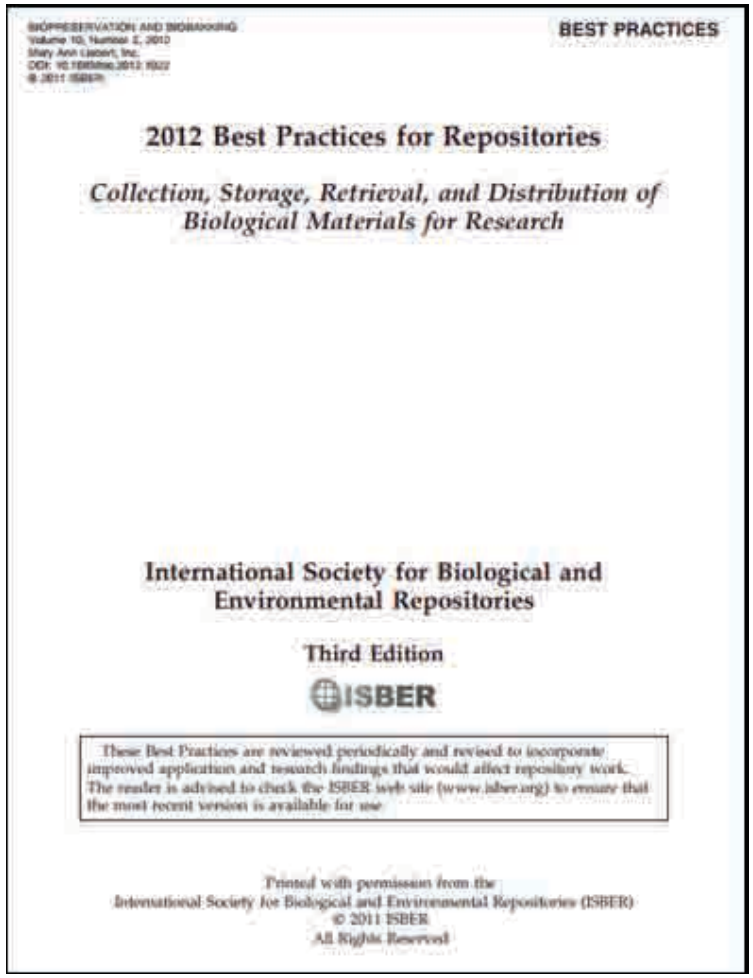
Repository Planning

- Facilities
- Storage Equipment And Environments
- Quality Management
- Safety
- Records Management
- Biological Material Tracking

Training

Cost Management & Sustainability

ISBER Best Practices for Repositories



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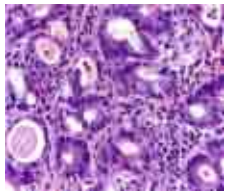
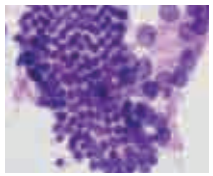
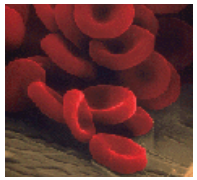
- **Communicates the most effective practices for the management of specimen collections and repositories**
- **Reflects the collective experience of its members and has received broad input from other repository professionals**

Banks of biological material collected from cancer patients and their use.


Bulk tissue


Cytologic preparations


Peripheral blood


Plasma


Urine

frozen

cryopreserved

paraffin

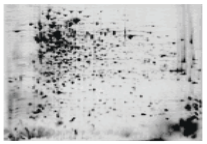
DNA: CGH analysis

in vivo model

Xenograft

RNA: expression profiling

Proteins : expression profiling



Selection of altered genes-proteins

gene expression analysis using antibodies or DNA probes


Tissue chip

Gastric tumor array

Selection of tumor types in which the expression of the given gene is altered

DNA

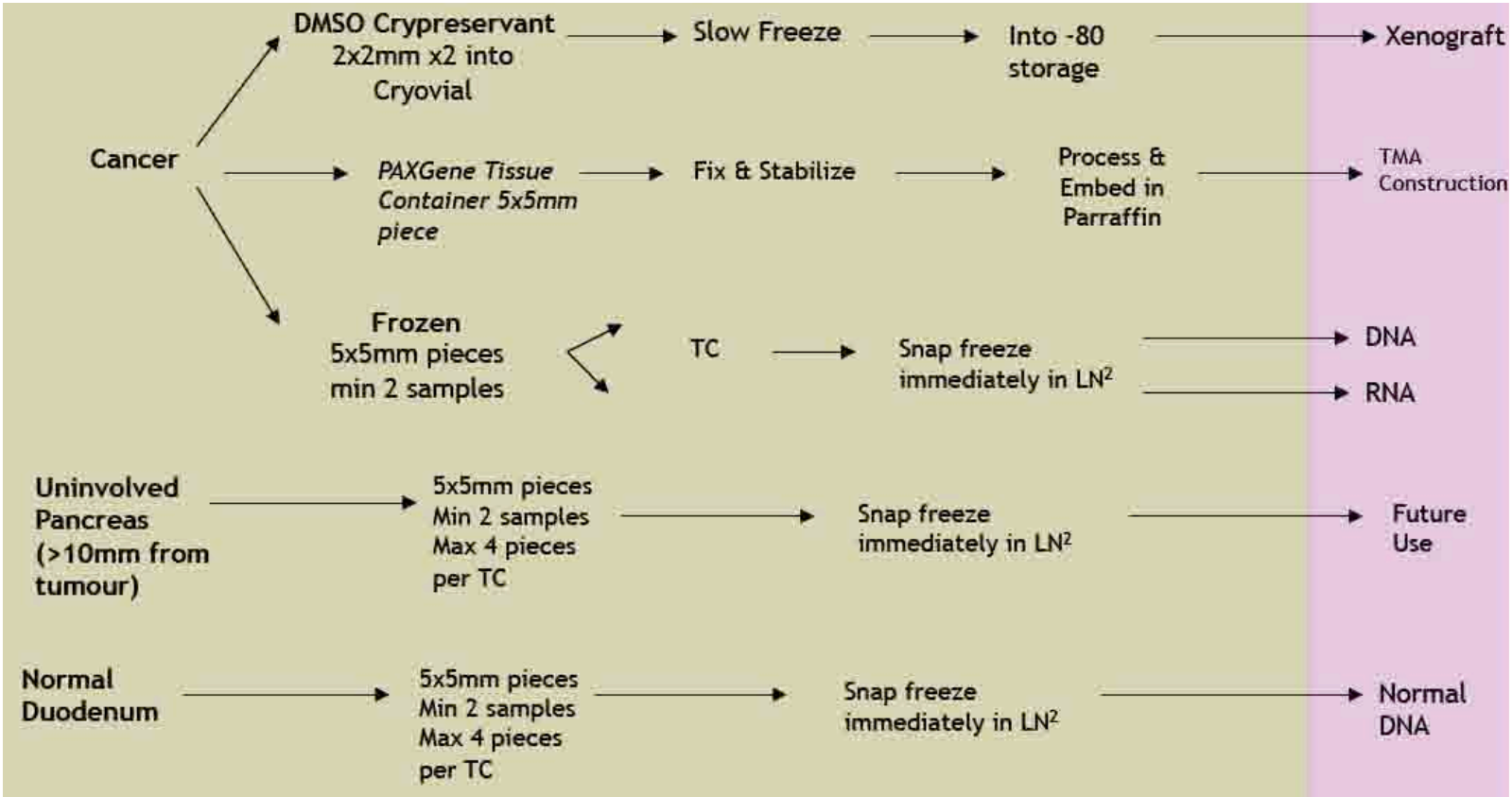
SNP analysis

Proteins

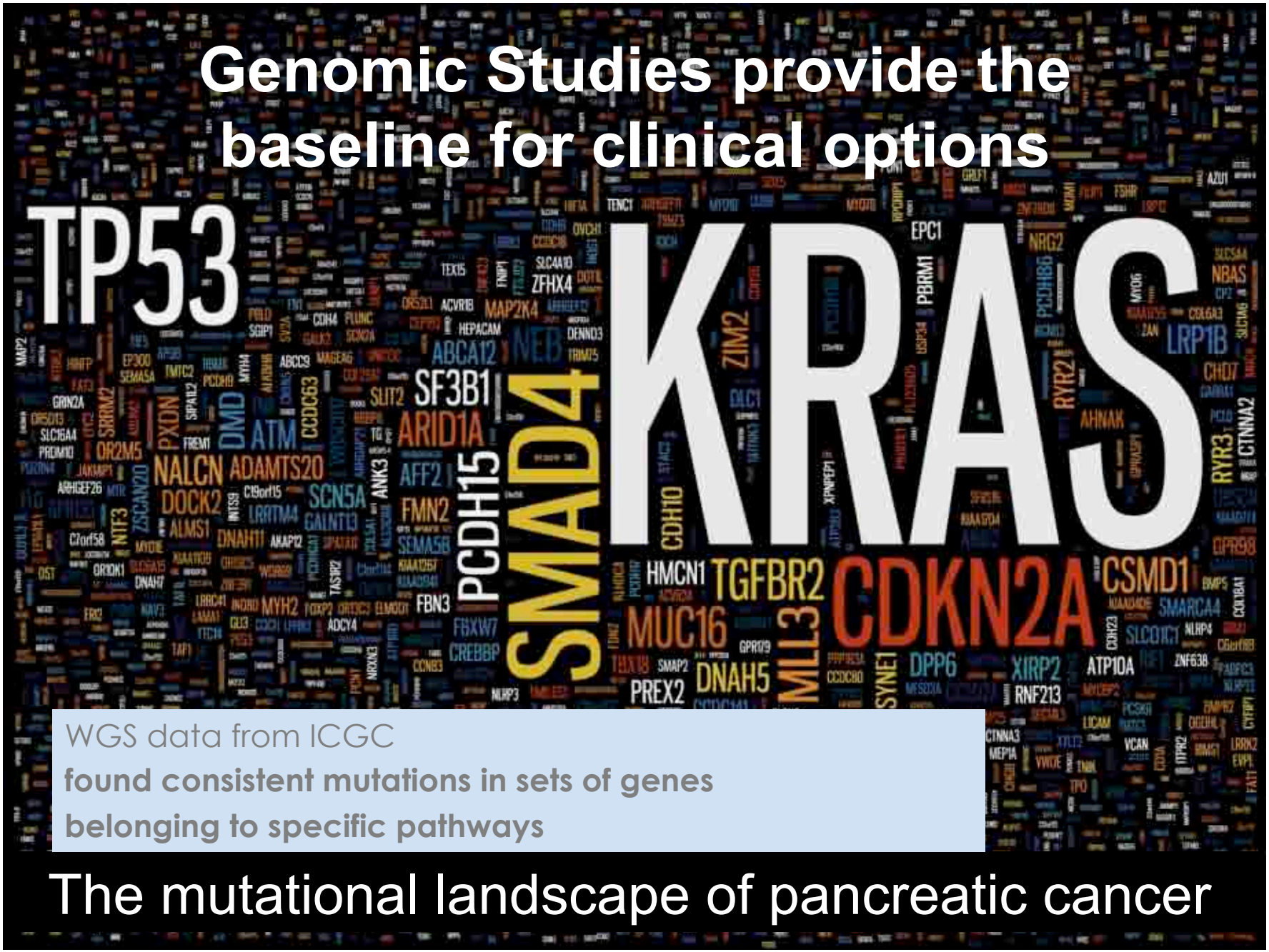
markers validation

Risk assessment and non invasive diagnosis

SURGERY **LABORATORY**



Genomic Studies provide the baseline for clinical options



WGS data from ICGC

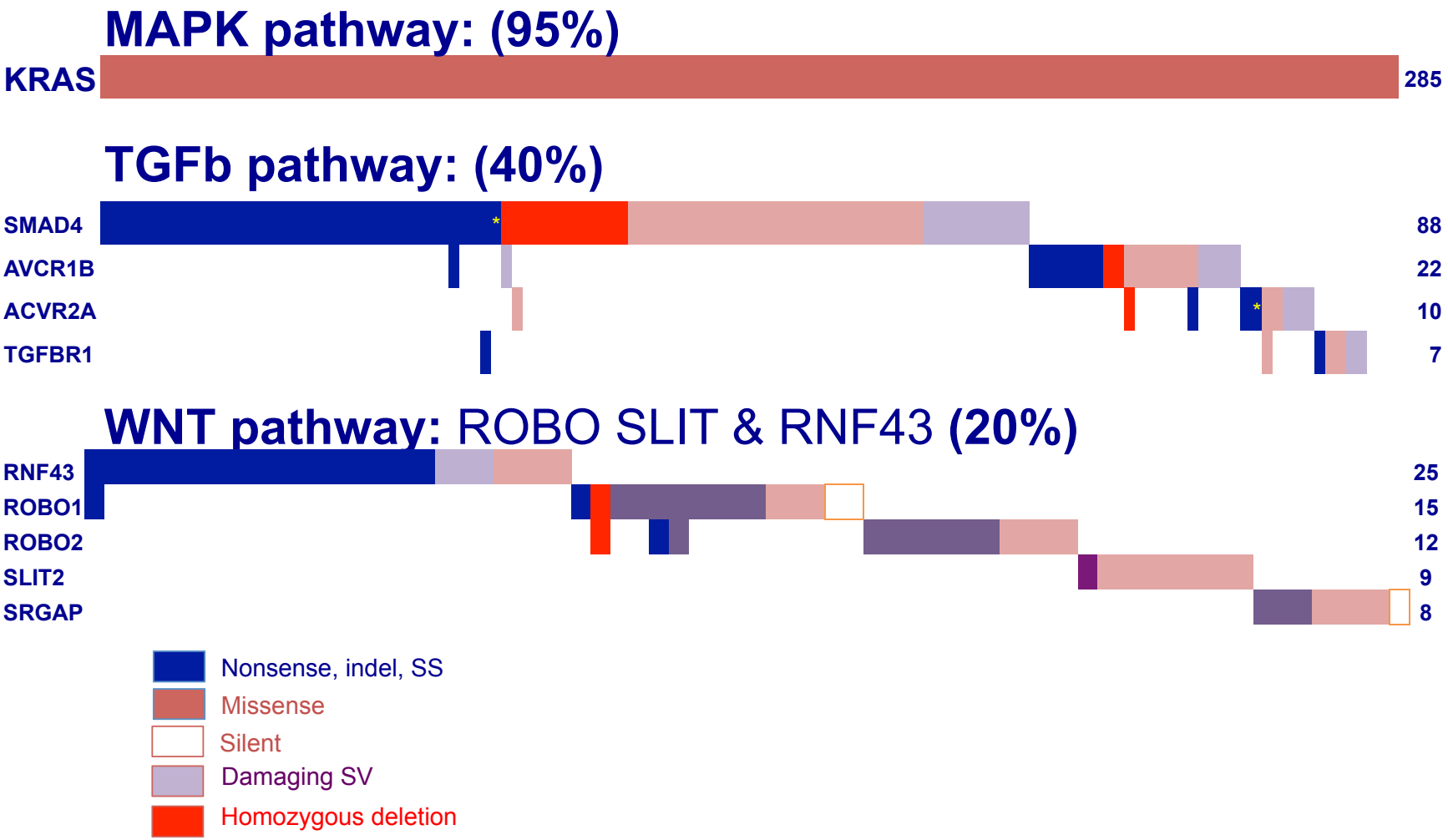
found consistent mutations in sets of genes

belonging to specific pathways

The mutational landscape of pancreatic cancer

Pancreas Cancer

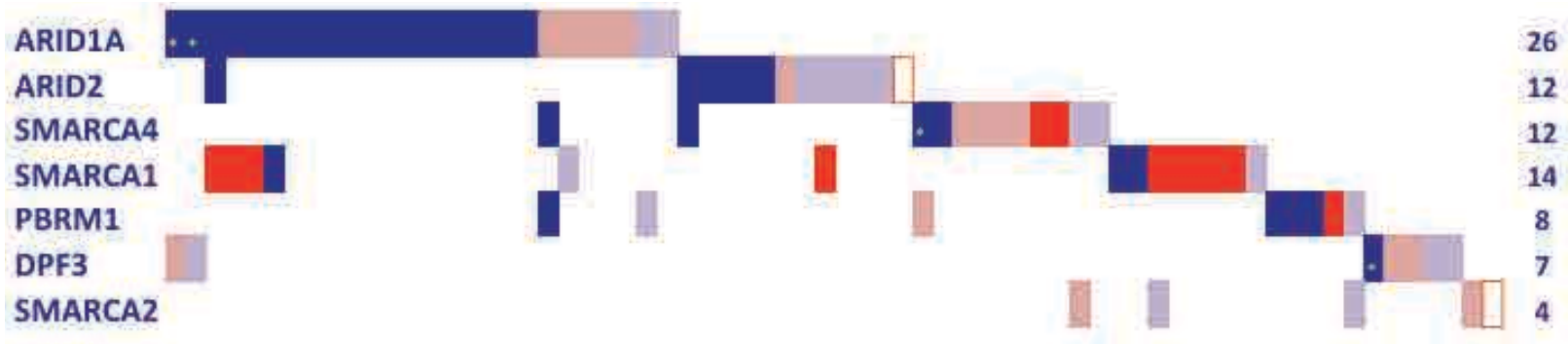
Pathway-specific signatures – 475 PDAC



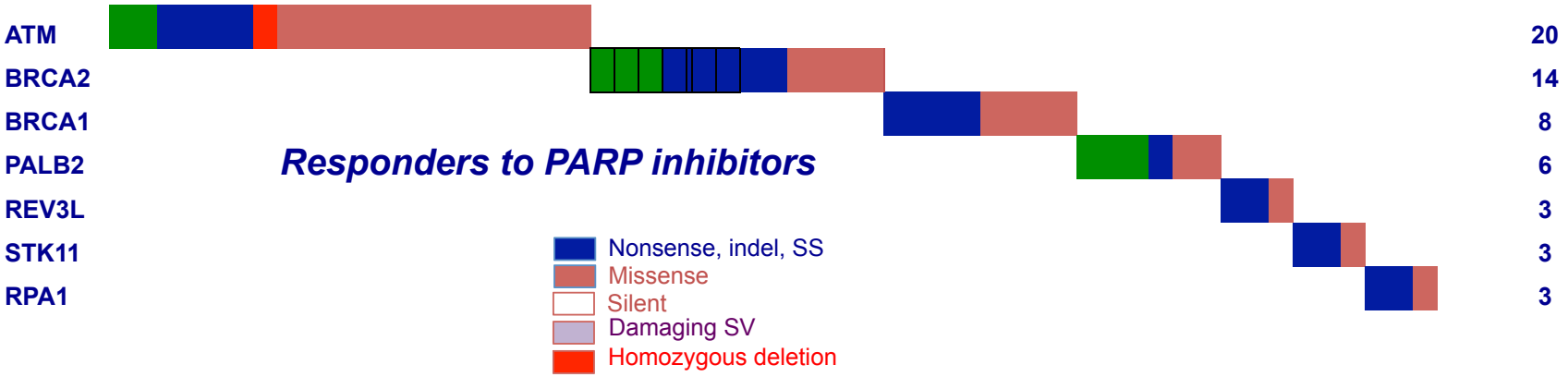
Pancreas Cancer

Pathway-specific signatures – 475 PDAC

SWI/SNF – Chromatin remodeling: (25%)

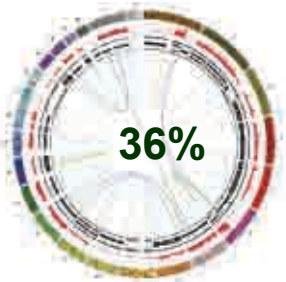


DNA Damage repair: (20%)



Whole genomes redefine the mutational landscape of PDAC

Stable
(<50 events)



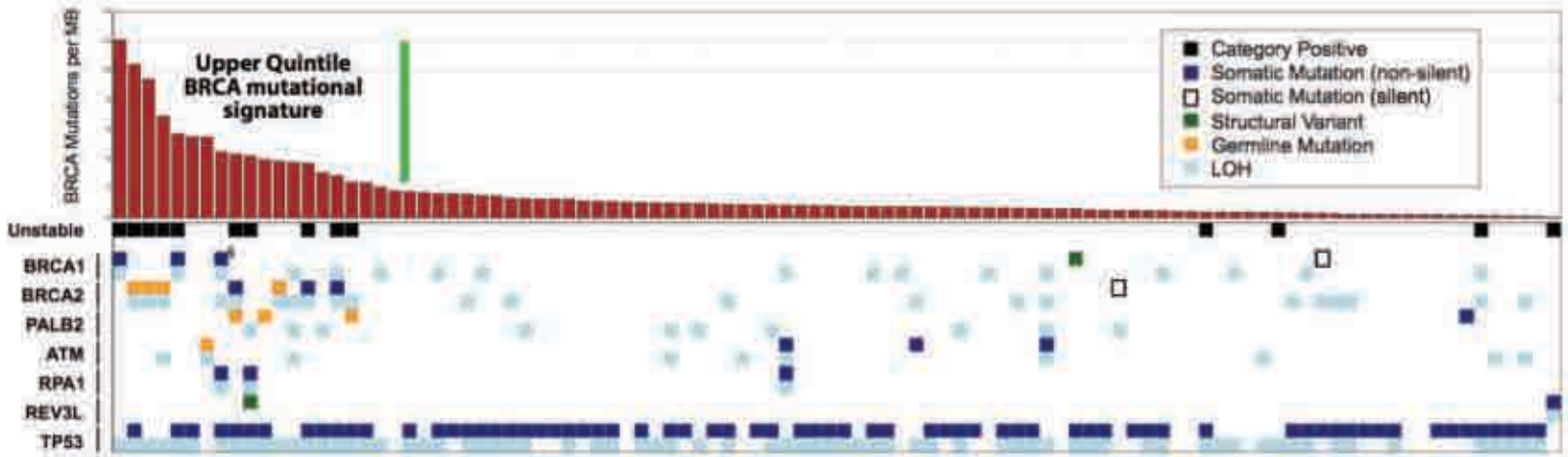
Scattered
(50 – 200 widespread)

Focal
(50-200, 50% on 1 Chr)

Unstable
(>200 widespread)

Waddell N, et al – Nature 2015

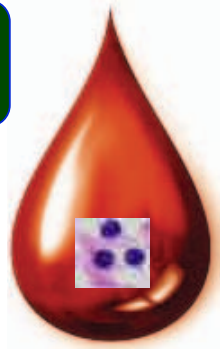
Unstable Genotype is associated with BRCA signature



Waddell N, et al – Nature 2015

Genomic information can define diagnostic and actionable subgroups for the clinic

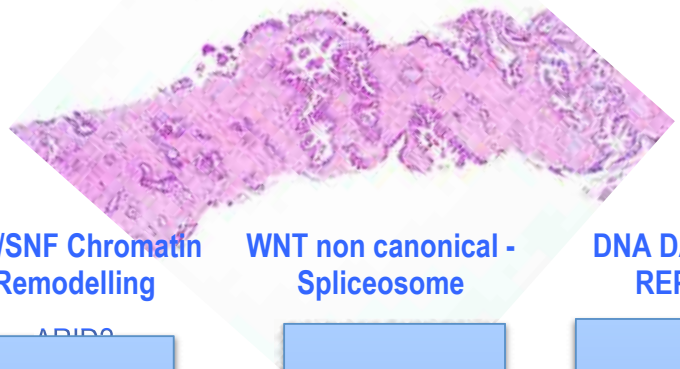
1. Diagnosis
2. Prognosis
3. Predict drug efficacy
4. Follow up



How do we apply this information to the clinic?

NGS – PDAC Gene panels
for pathway based molecular diagnostics

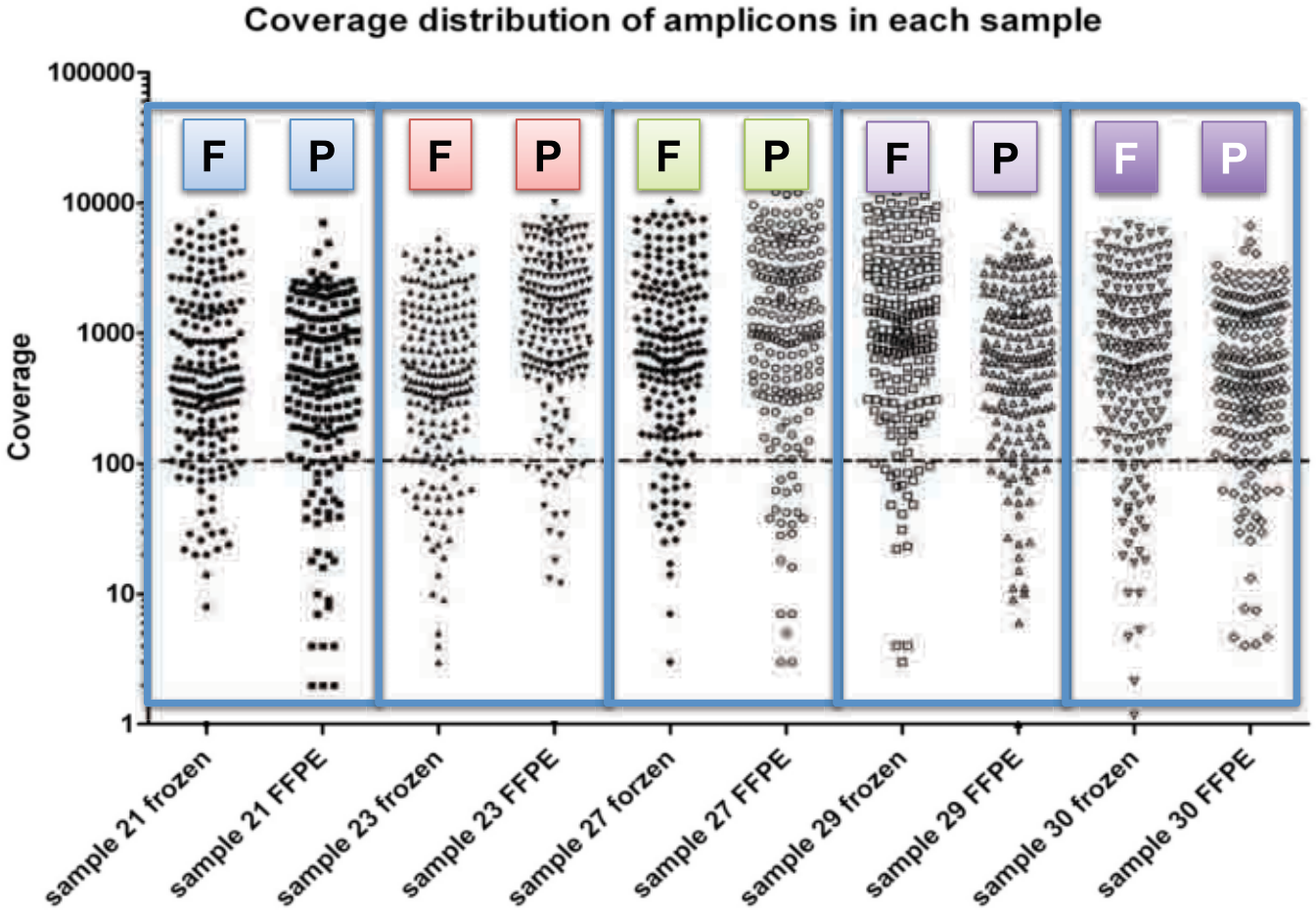
1 **Diagnosis**



Panel Name	PDAC periampullary basic	TGFB Pathway	SWI/SNF Chromatin Remodelling	WNT non canonical - Spliceosome	DNA DAMAGE REPAIR
GENES	KRAS BRAF NRAS GNAS BBB CCC DDD EEE FFF GGG HHH	SMAD 4	BAP1 ARID2 BBB CCC DDD EEE FFF GGG HHH	ROBO1 SLIT2 BBB CCC DDD EEE FFF GGG HHH	BRCA1 BRCA2 BBB CCC DDD EEE FFF GGG HHH

NGS FROZEN and FFPE
High quality of DNA sequences

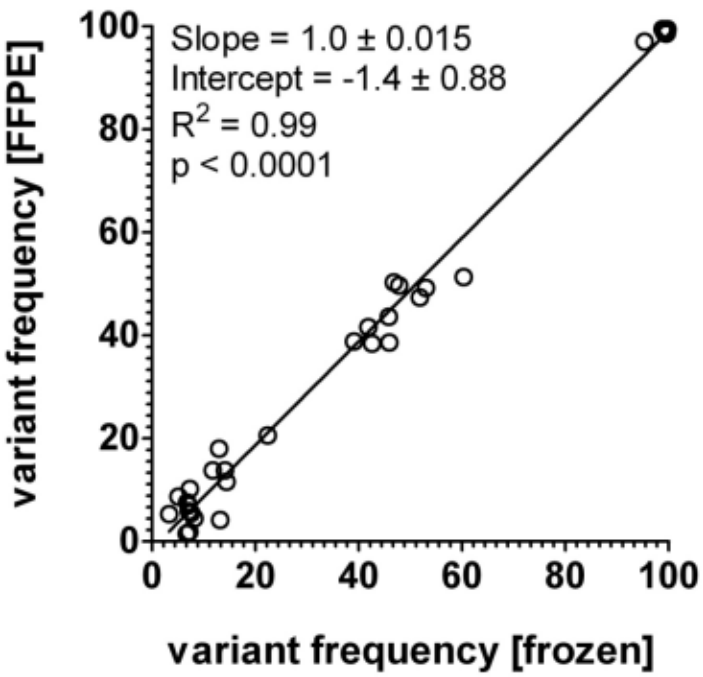
1 Diagnosis



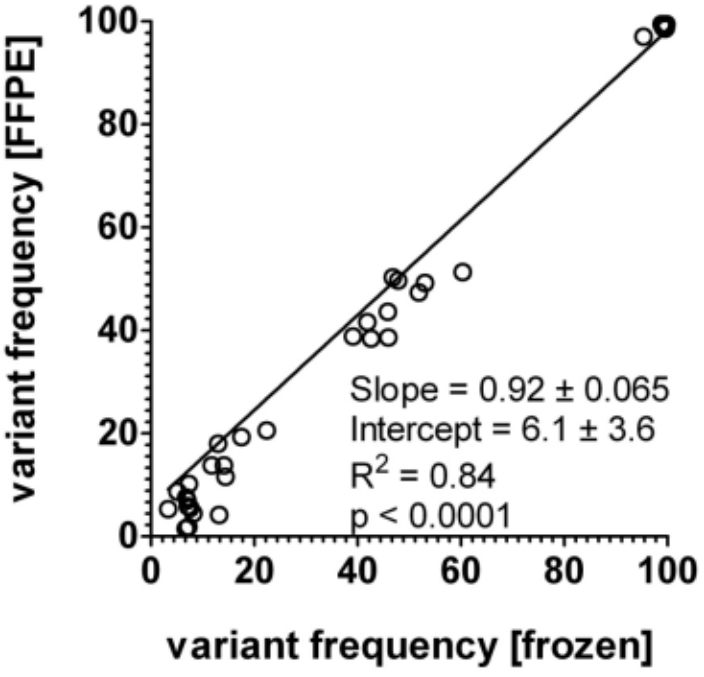
Mutations in FROZEN and FFPE samples coincide

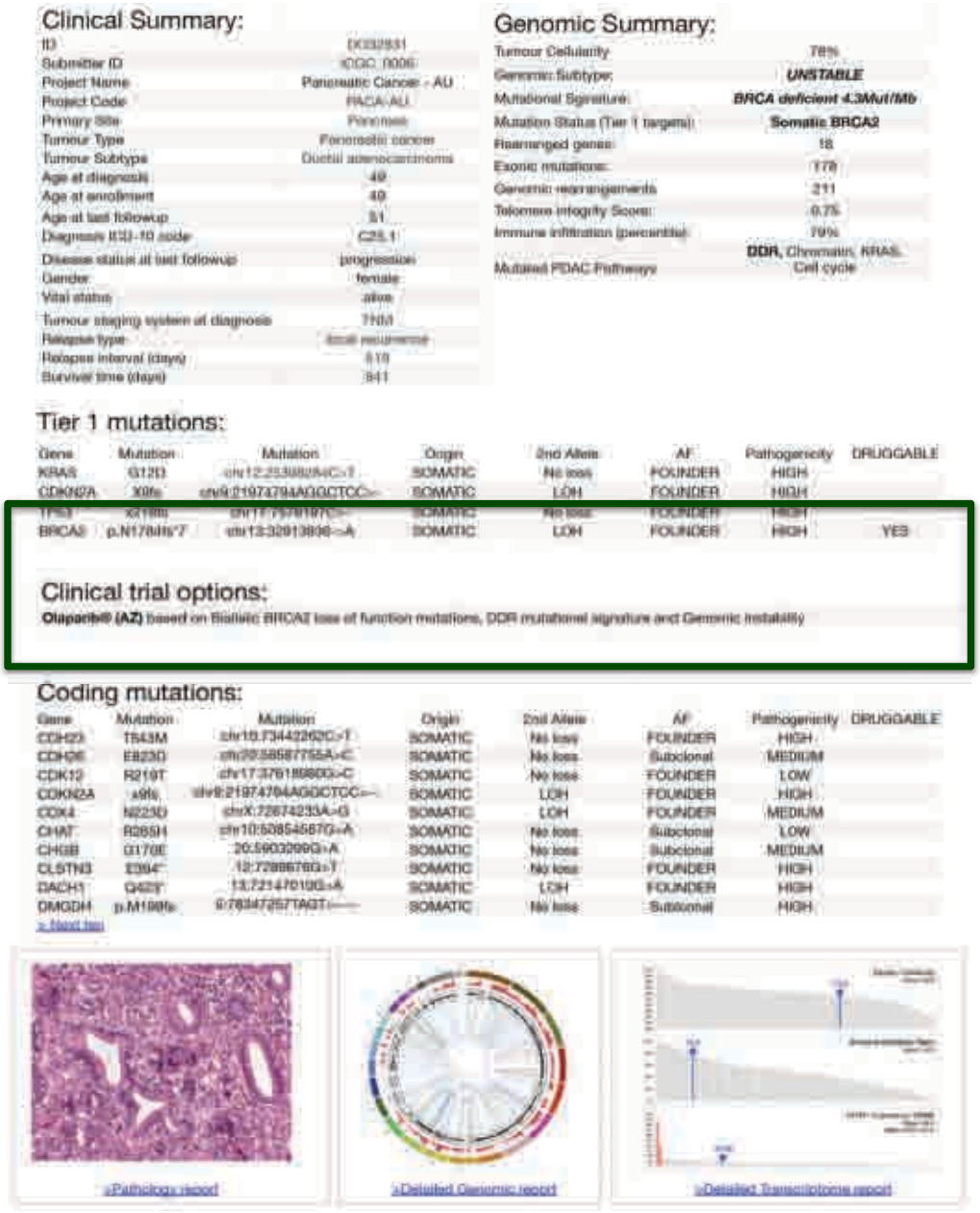
1 Diagnosis

point mutations



Insertions/ deletions





Clinical Summary:

ID	DO32831
Submitter ID	ICGC_0006
Project Name	Pancreatic Cancer - AU
Project Code	PACA-AU
Primary Site	Pancreas
Tumour Type	Pancreatic cancer
Tumour Subtype	Ductal adenocarcinoma
Age at diagnosis	49
Age at enrollment	49
Age at last followup	51
Diagnosis ICD-10 code	C25.1
Disease status at last followup	progression
Gender	female
Vital status	alive
Tumour staging system at diagnosis	TNM
Relapse type	local recurrence
Relapse interval (days)	519
Survival time (days)	841

Genomic Summary:

Tumour Cellularity	78%
Genomic Subtype:	***UNSTABLE***
Mutational Signature:	***BRCA deficient 4.3Mut/Mb***
Mutation Status (Tier 1 targets):	**Somatic BRCA2**
Rearranged genes:	18
Exonic mutations:	178
Genomic rearrangements	211
Telomere integrity Score:	0.75
Immune infiltration (percentile)	79%
Mutated PDAC Pathways	**DDR**, Chromatin, KRAS, Cell cycle

Tier 1 mutations:

Gene	Mutation	Mutation	Origin	2nd Allele	AF	Pathogenicity	DRUGGABLE
KRAS	G12D	chr12:25380284C>T	SOMATIC	No loss	FOUNDER	HIGH	
CDKN2A	X0fs	chr9:21974794AGGCTCC>-	SOMATIC	LOH	FOUNDER	HIGH	
TP53	X218fs	chr17:7578197C>-	SOMATIC	No loss	FOUNDER	HIGH	
BRCA2	p.N178fs*7	chr13:32913896>A	SOMATIC	LOH	FOUNDER	HIGH	YES

Clinical trial options:

Olaparib® (AZ) based on Biallelic BRCA2 loss of function mutations, DDR mutational signature and Genomic instability

Coding mutations:

Gene	Mutation	Mutation	Origin	2nd Allele	AF	Pathogenicity	DRUGGABLE
CDH23	T543M	chr10:73442262C>T	SOMATIC	No loss	FOUNDER	HIGH	
CDH26	E823D	chr20:58587755A>C	SOMATIC	No loss	Subclonal	MEDIUM	
CDK12	R219T	chr17:37618880G>C	SOMATIC	No loss	FOUNDER	LOW	
CDKN2A	x9fs,	chr9:21974794AGGCTCC>-	SOMATIC	LOH	FOUNDER	HIGH	
CDK4	N223D	chrX:72674233A>G	SOMATIC	LOH	FOUNDER	MEDIUM	
CHAT	R265H	chr10:50854567G>A	SOMATIC	No loss	Subclonal	LOW	
CHGB	G170E	20:5903299G>A	SOMATIC	No loss	Subclonal	MEDIUM	
CLSTN3	E394*	12:72886780>T	SOMATIC	No loss	FOUNDER	HIGH	
DACH1	G423*	13:72147010G>A	SOMATIC	LOH	FOUNDER	HIGH	
DMGDH	p.M198fs	6:78347257TAGT>-	SOMATIC	No loss	Subclonal	HIGH	

» Next ten

» Pathology report

» Detailed Genomic report

» Detailed Transcriptome report

Molecular Phenotype Report

with

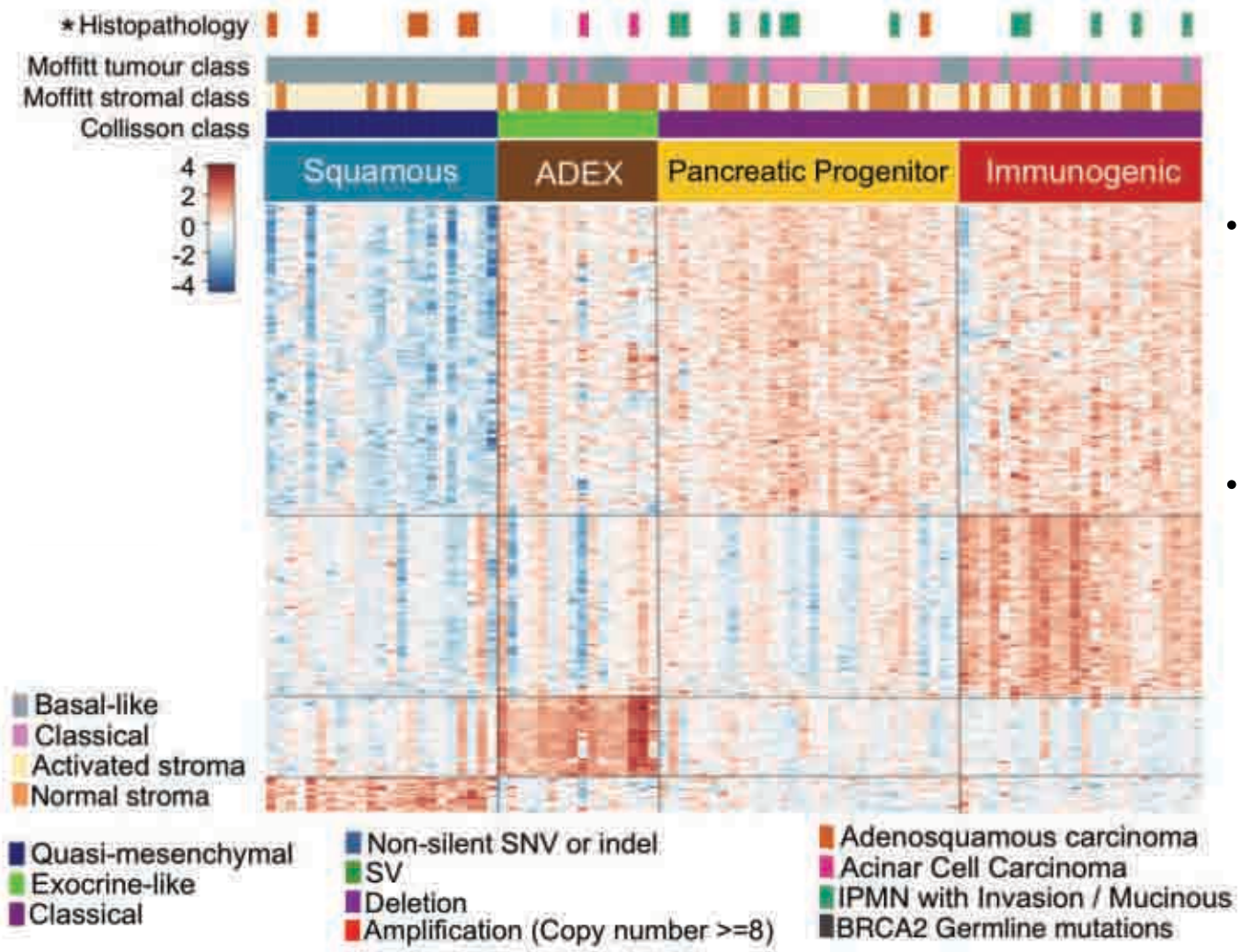
Clinical Trial Options

1 **Diagnosis**

NEXT GENERATION HISTO-PATHOLOGY

1 Diagnosis

RNAseq (N = 96)

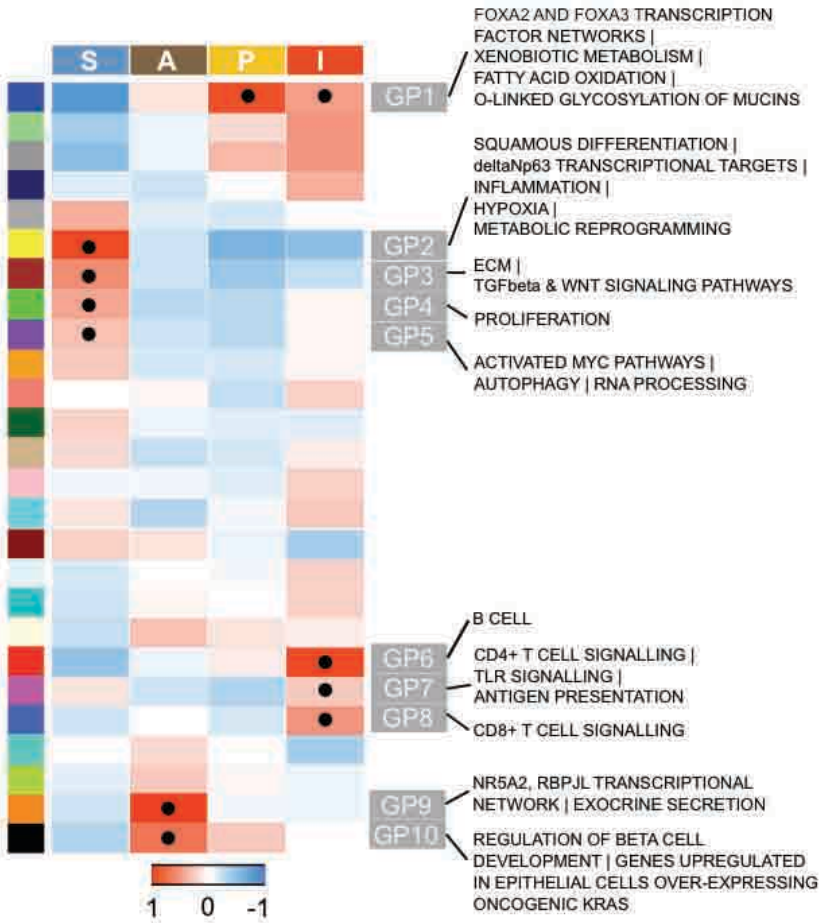


- 4 classes based on transcription factors and downstream targets
- Enriched with specific histological features

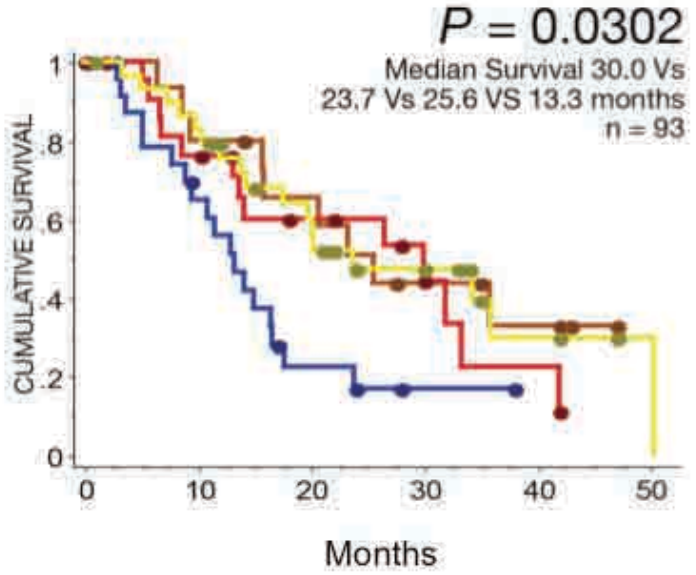
Bailey *et al*, (in print)

1 Diagnosis

Molecular Subtypes of PDAC



- Squamous subtype worst prognosis
- Transcriptional network analysis identified 10 core gene programmes associated with different classes



Bailey *et al*, (in print)

Mutations in 79 primary PDAC

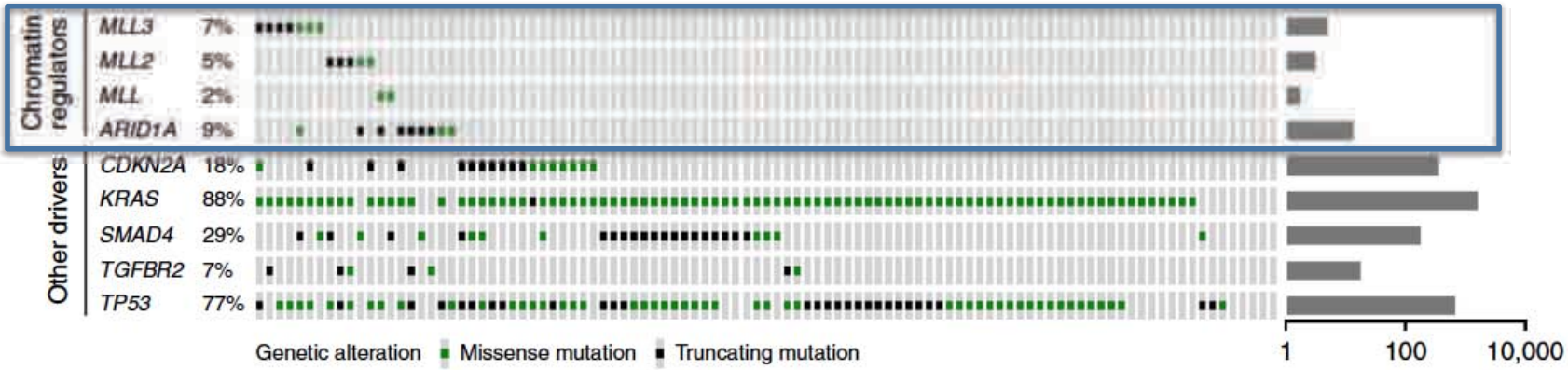
Chromatin remodelling (15-genes)

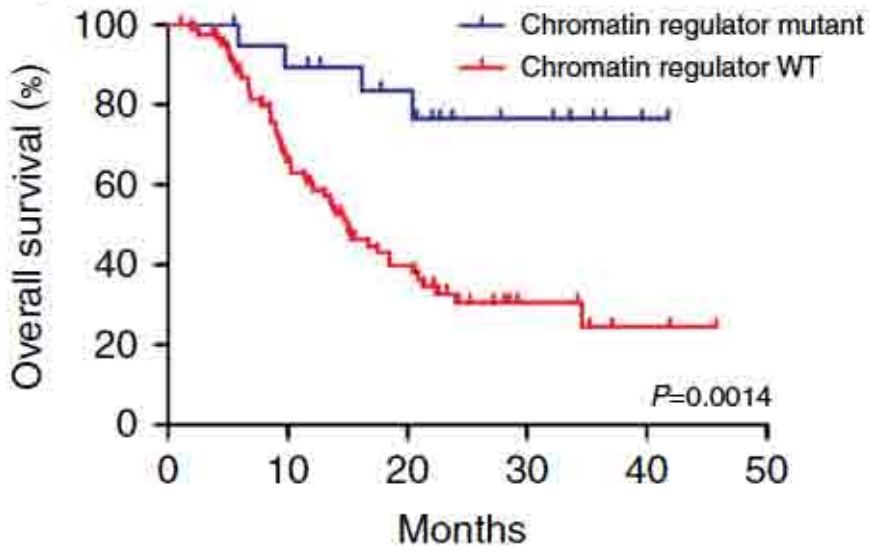
Gene	Pathogenic
BAP1	8
ARID2	1
BBB	1
CCC	1
DDD	2
EEE	4
FFF	3
GGG	1
HHH	2
IIII	1
JJJ	1
KKK	2
Total	27 (21%)

2 **Prognosis**

A total of 27 cases mutated = 34%

Chromatin remodelling and prognosis





2 **Prognosis**

Sausen M et al. *Nature Communications*. 2015

Mutations in 79 primary PDAC

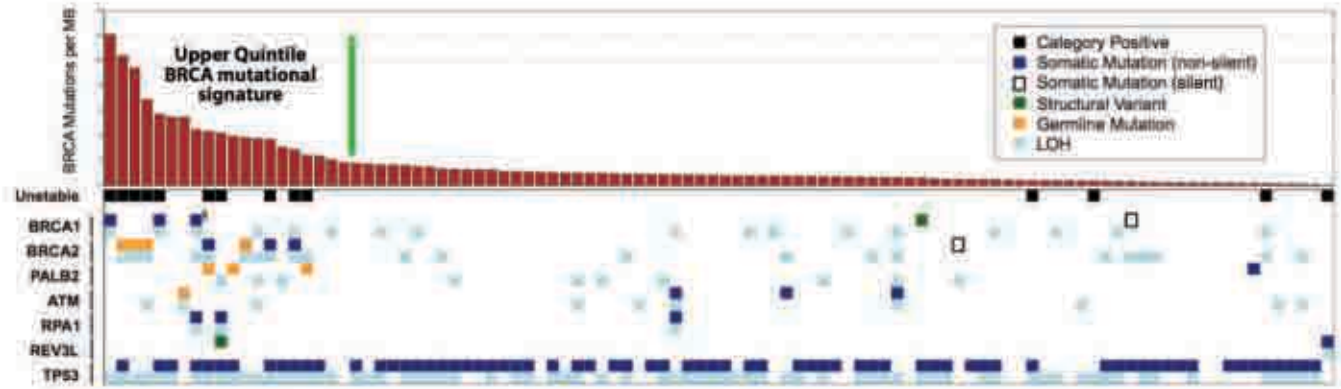
BRCAness pathogenic mutations

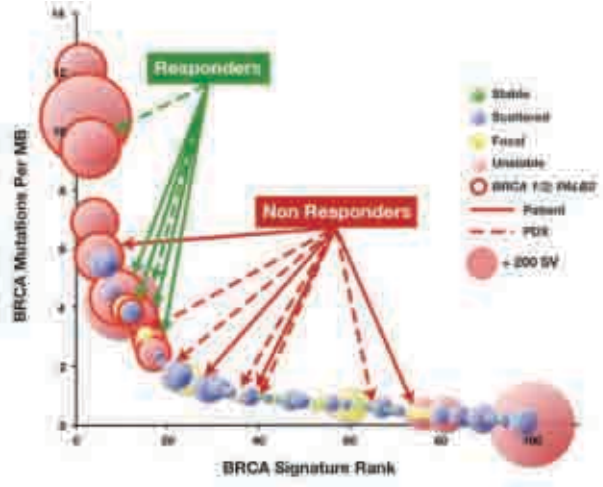
Gene	Pathogenic
XXX	3
BRCA1	**3**
BRCA2	**9**
PALB2	**1**
CCC	3
DDD	1
EEE	2
FFF	2
GGG	1
HHH	
III	
Total	25

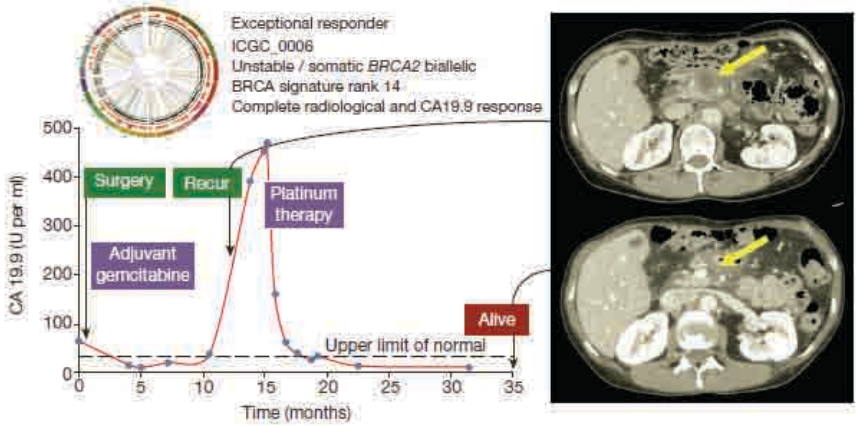
3 **Predict drug efficacy**

A total of 25 cases mutated (32%)

Unstable Genotype is associated with BRCA signature

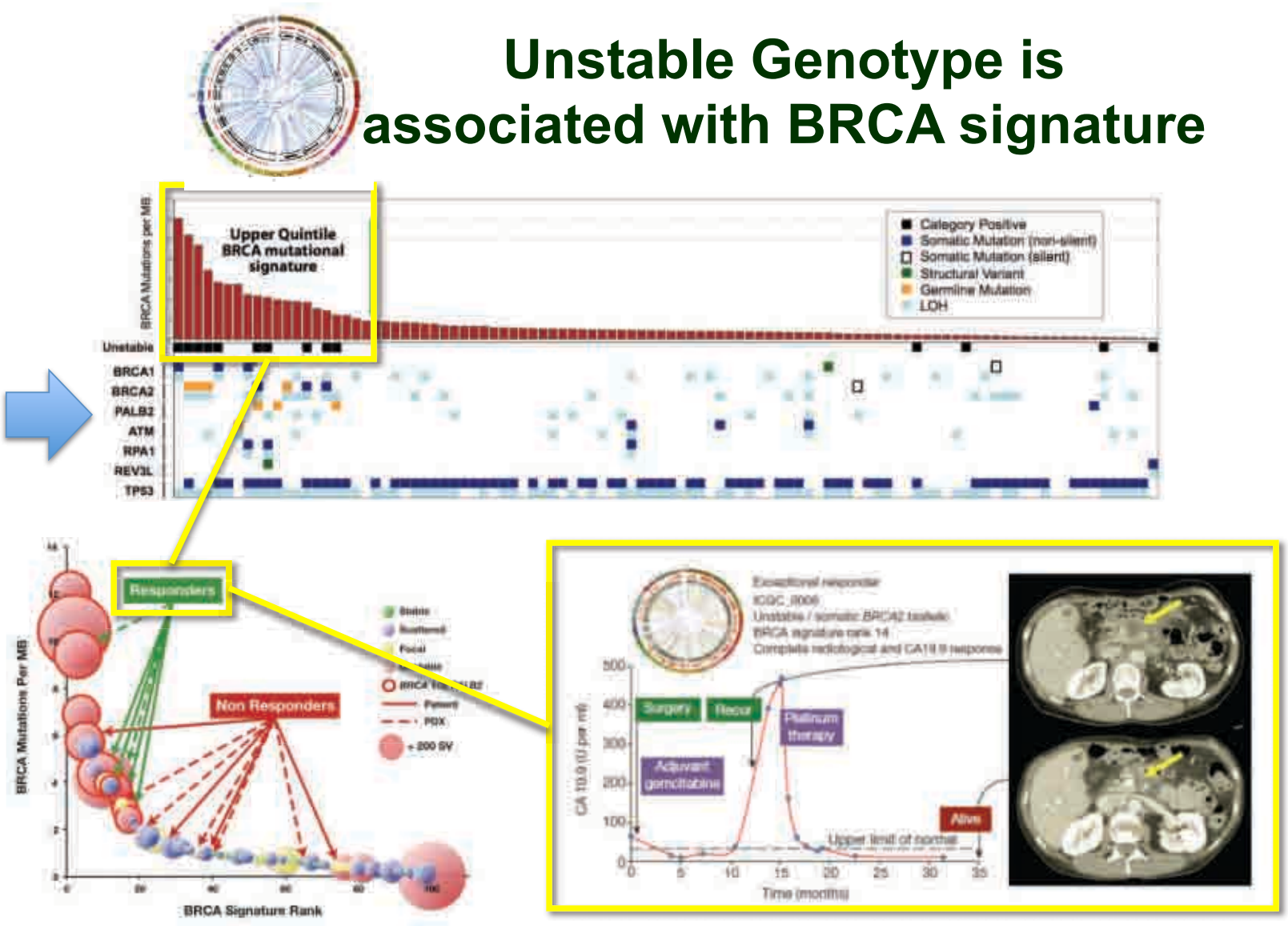






Waddell N, et al – Nature 2015

Unstable Genotype is associated with BRCA signature



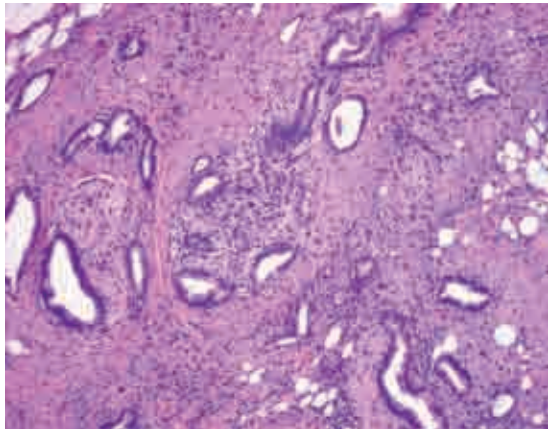
Waddell N, et al – Nature 2015

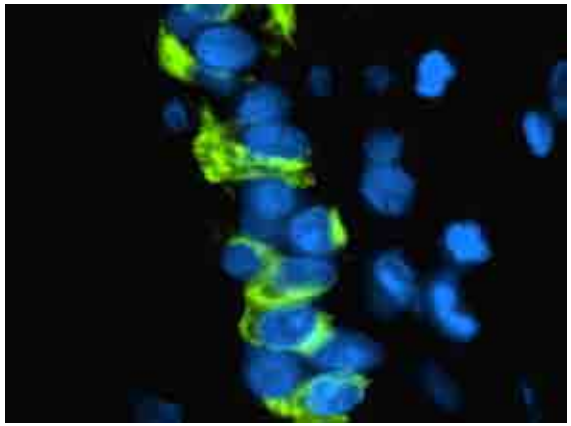
4 Follow up

Tumor Burden

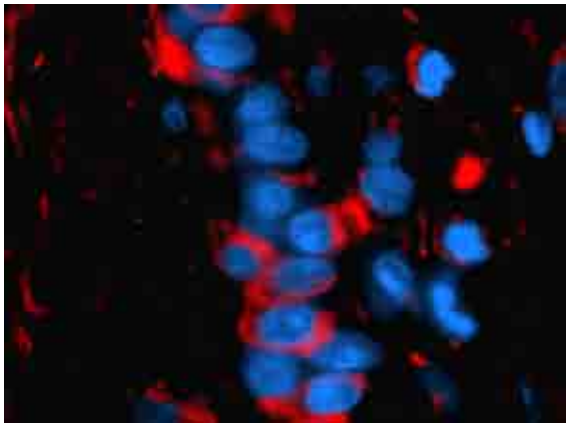
Pancreatic cancer cellularity

Sample	Cell	*KRAS*
1	15%	G12R (60%)

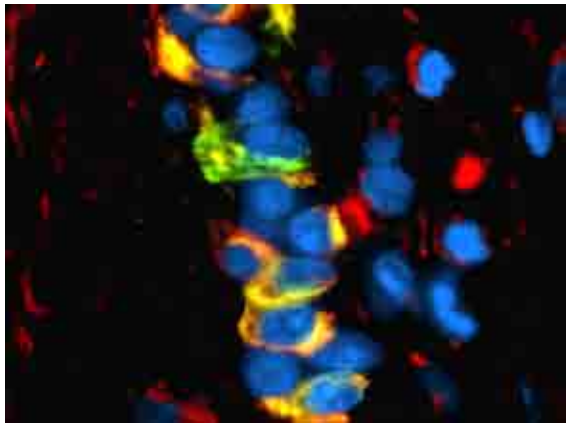




Keratin

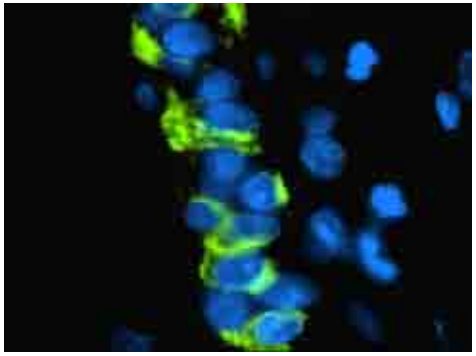


Vimentin



Fusion

Resolving FFPE Intratumoral Heterogeneity



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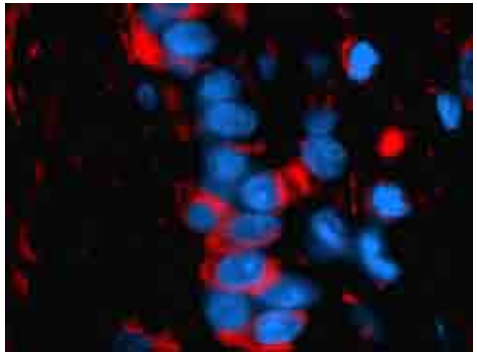

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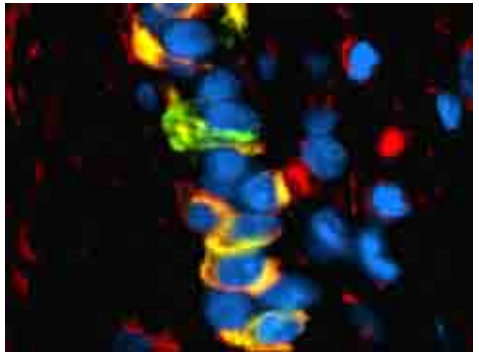
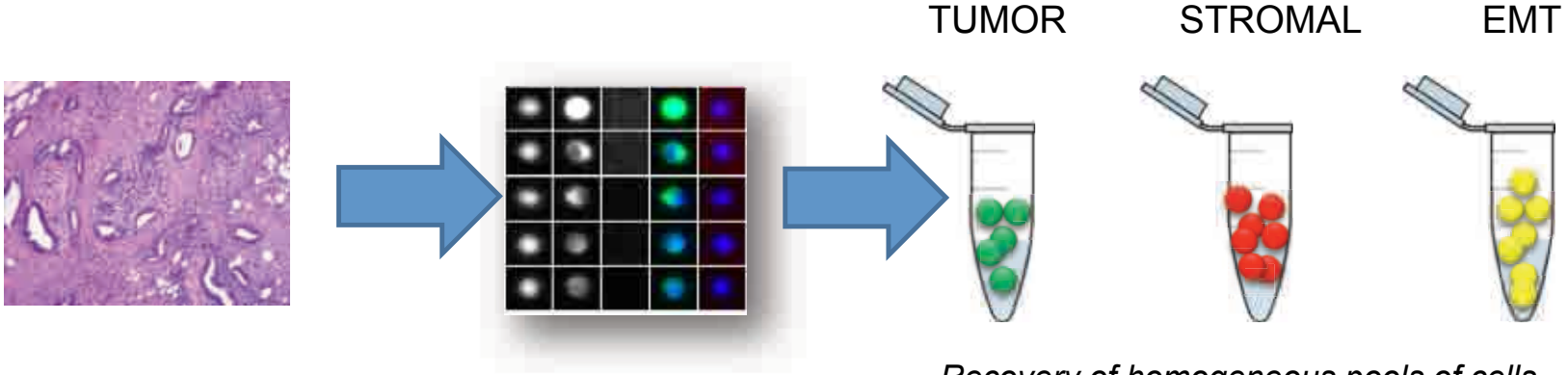
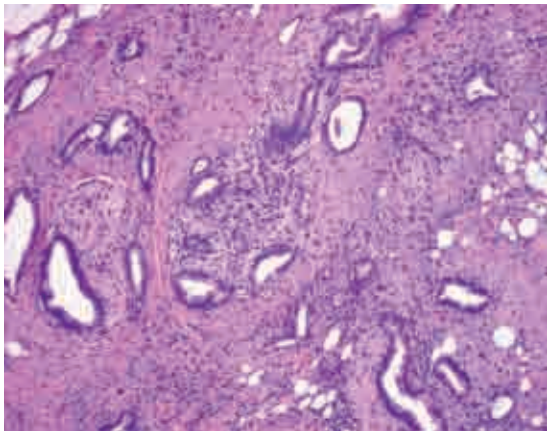


Fusion

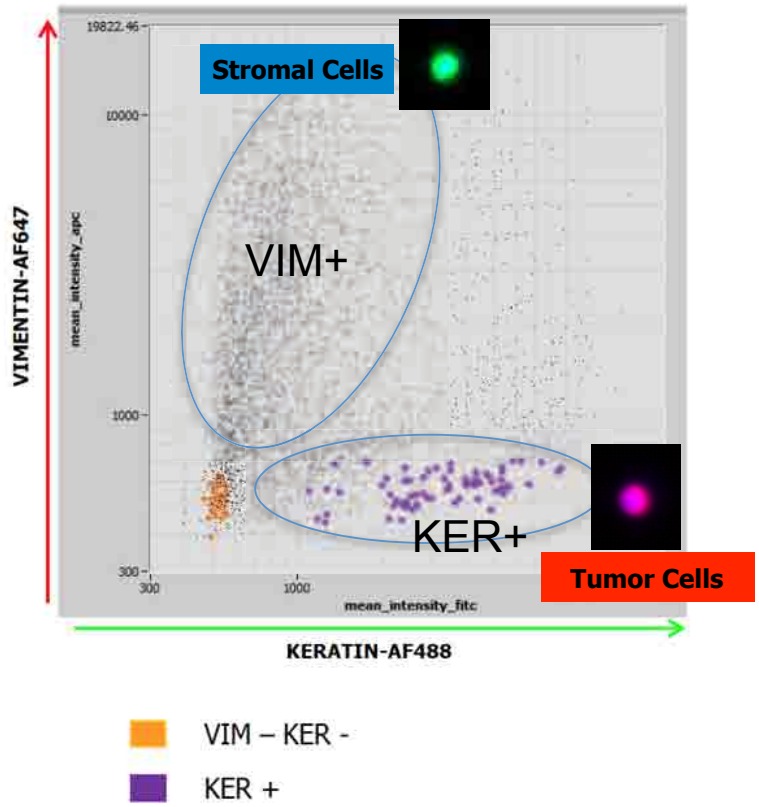


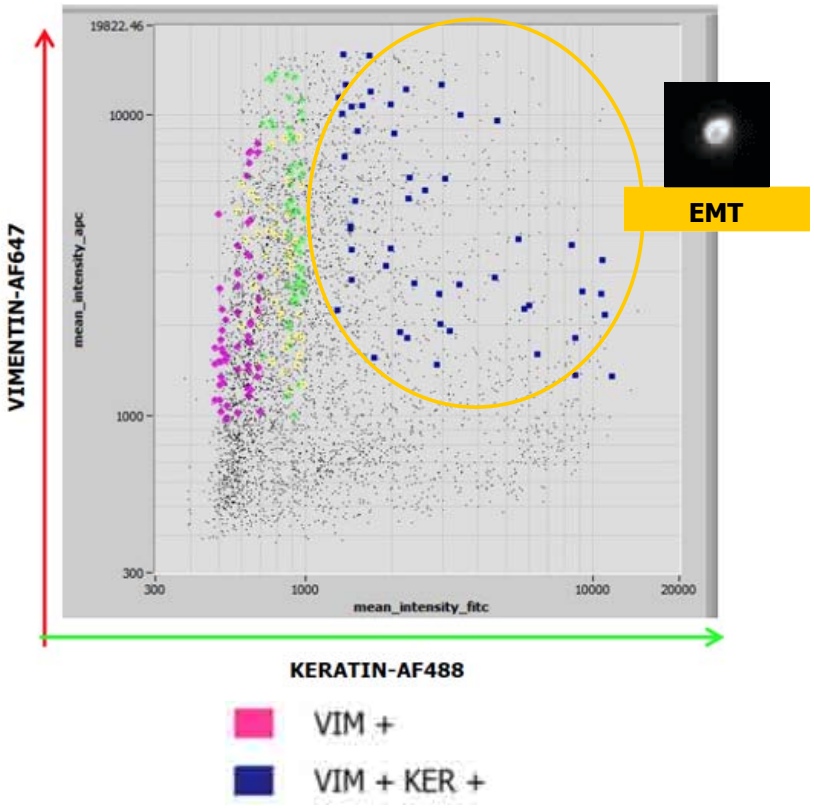
Recovery of homogeneous pools of cells

4 Follow up

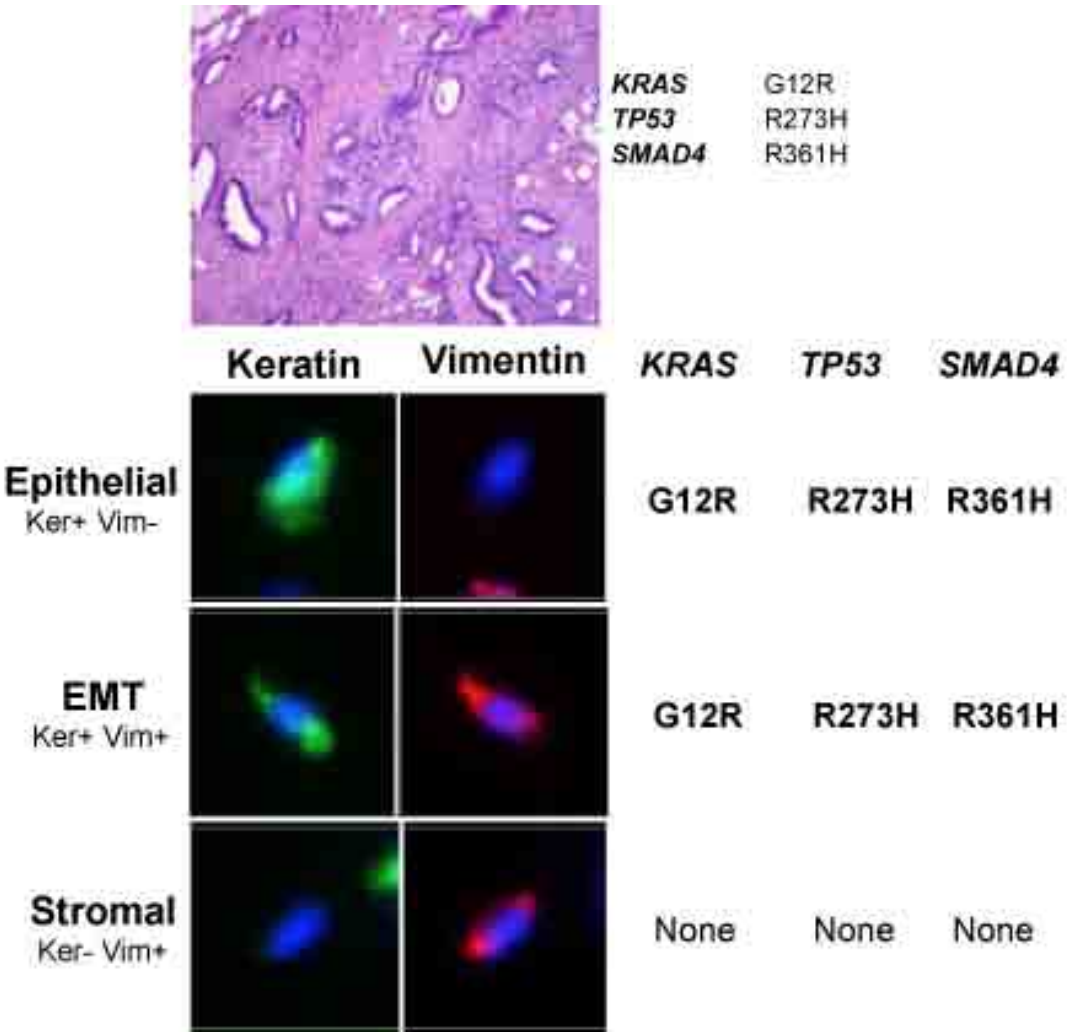


KRAS	G12R
TP53	R273H
SMAD4	R361H



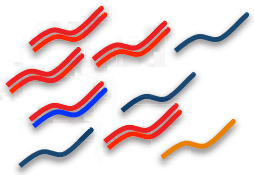


4 Follow up

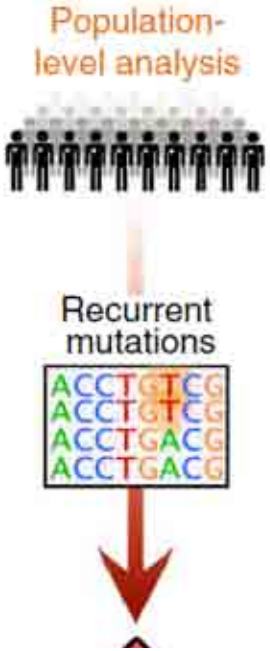

KRAS G12R
TP53 R273H
SMAD4 R361H
Keratin
Vimentin
KRAS
TP53
SMAD4
Epithelial
Ker+ Vim-
G12R R273H R361H
EMT
Ker+ Vim+
G12R R273H R361H
Stromal
Ker- Vim+
None None None

4 **Follow up**

Liquid biopsy: cfDNA

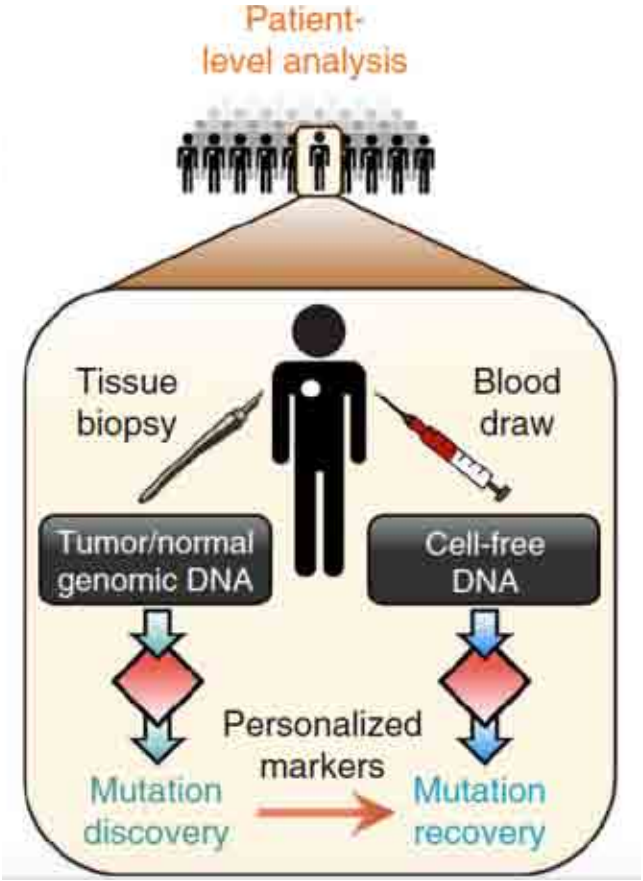


- ***Early diagnosis***



lack of specificity

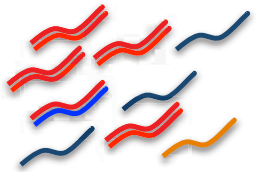
- ***Disease monitoring***



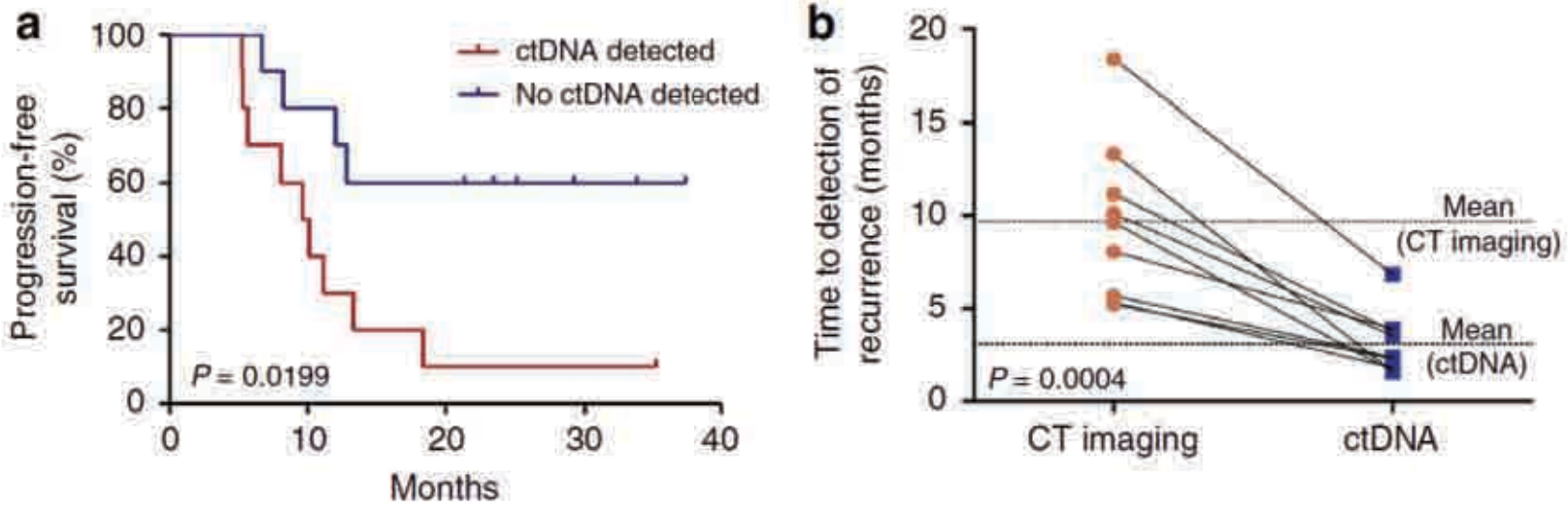
Newman AM et al. Nature Medicine. 2013

Pancreatic cancer: cfDNA

4 **Follow up**



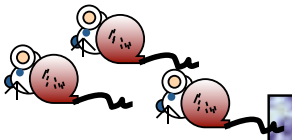
- dPCR detected alterations at diagnosis (specificity 99.9%)
- ctDNA detected recurrence before CT

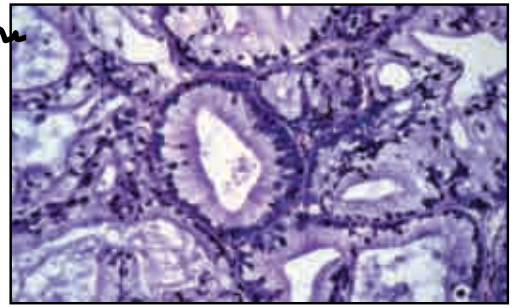
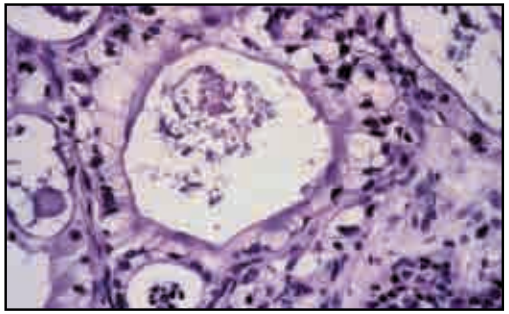
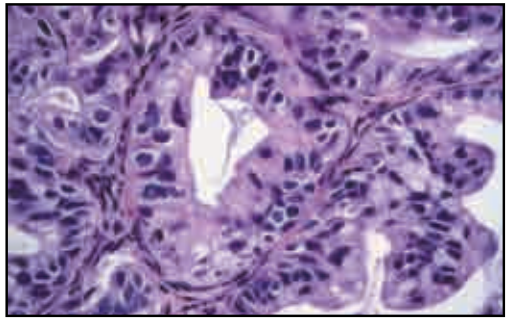
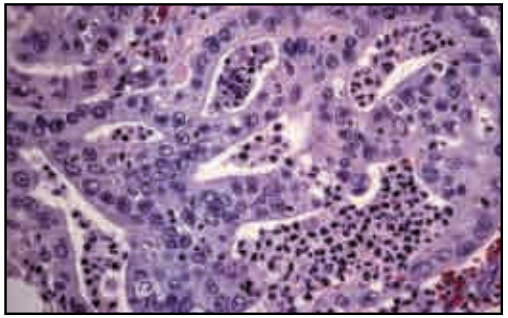
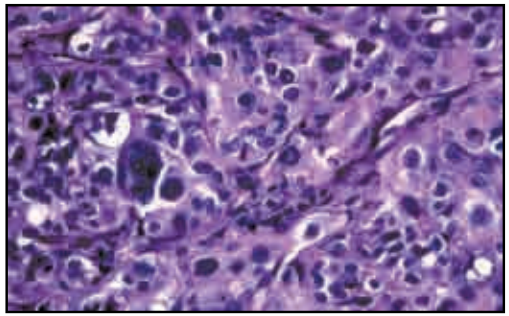
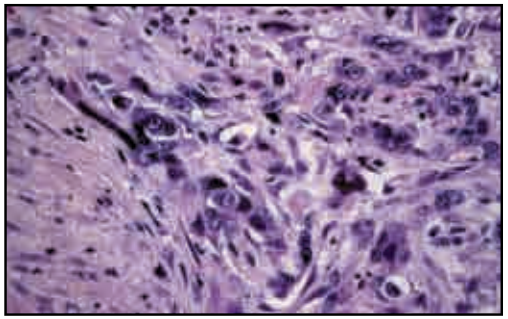


Sausen M et al. *Nature Communications*. 2015


Mission impossible?

Xenografts retain the morphology of the patient cancer



	Xenograft	Primary
PDX1		
PDX9		
PDX7		

October 2015

Mutations in 79 primary /xenografts pairs

PDAC / periampullary panel (17-genes)

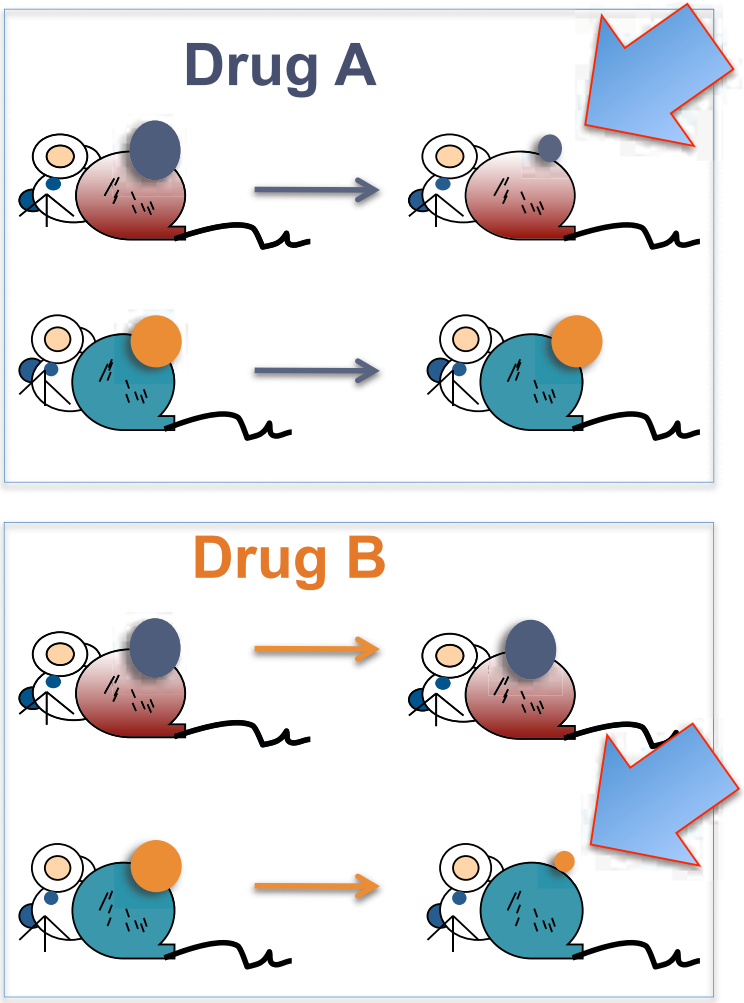
Gene	Mutated cases	Proportion
KRAS	75	95%
TP53*	51	64%
SMAD4**	19	24%
CDKN2A/p16	10	12%
GNAS	3	4%
APC	2	2.5%
FBXW7	1	1%
PIK3CA	1	1%

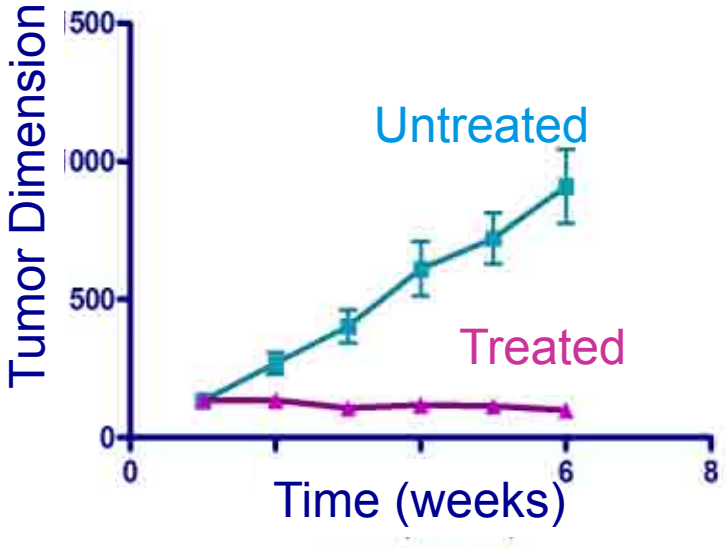
*IHC confirms the proportion

**IHC shows a higher proportion of inactivation

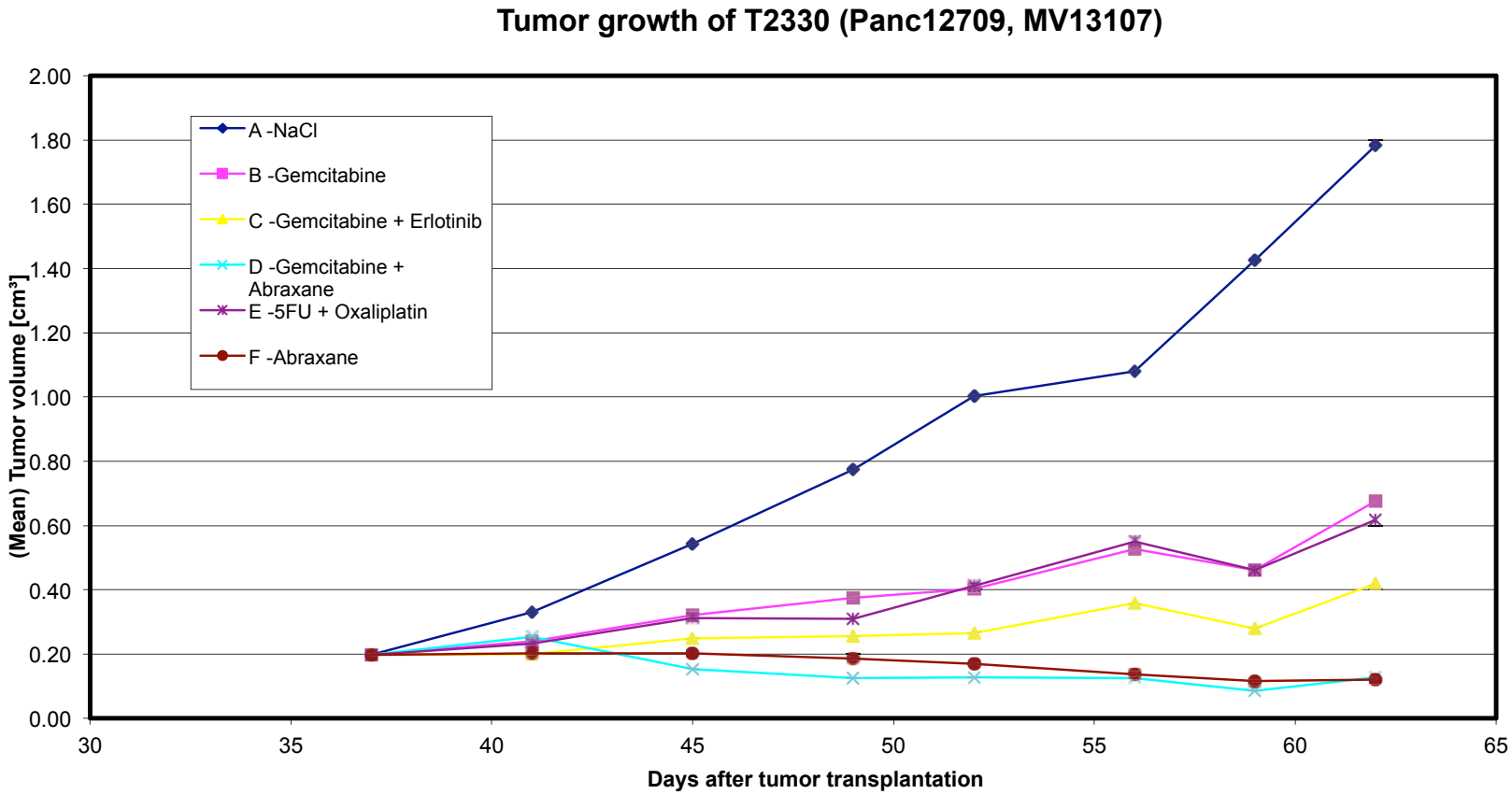
The analysis suggest non correspondence that is resolved or amplified in xenografts

Testing drugs on patient xenografts



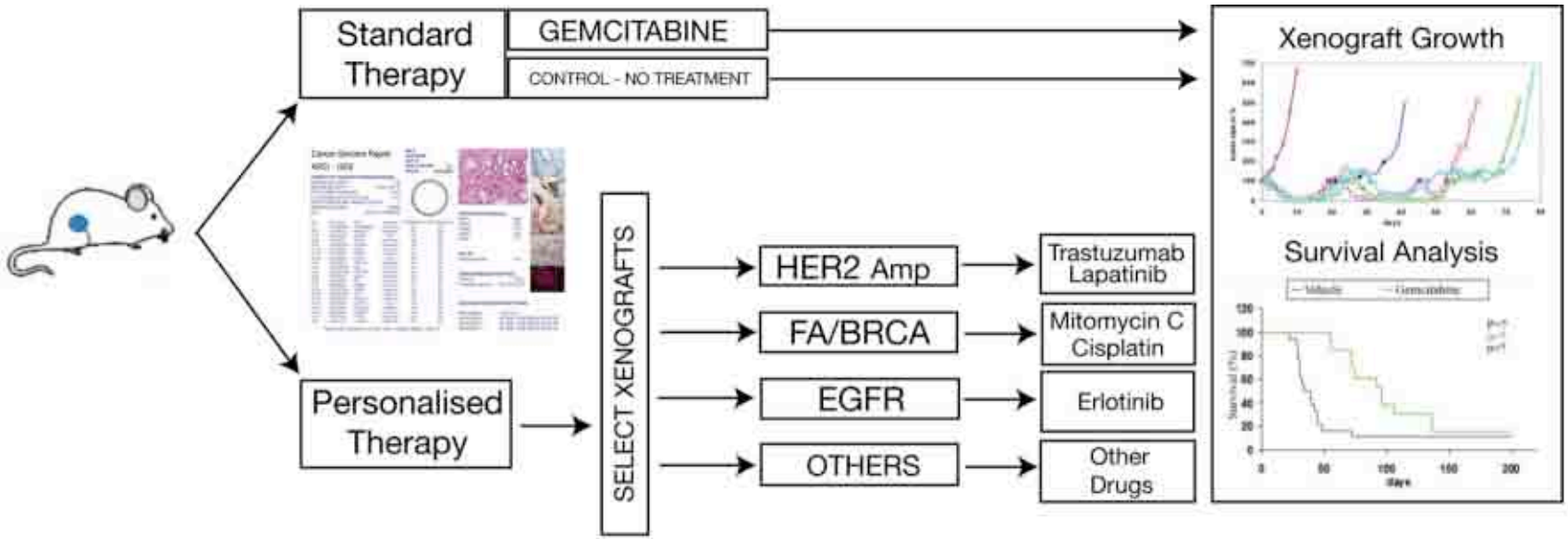


G2 - KRAS, P16, SMAD4, TP53, ACVR2A
- RBM10, SRGAP2

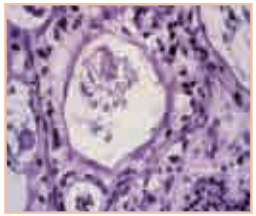
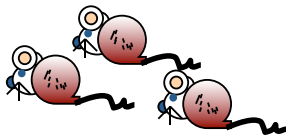
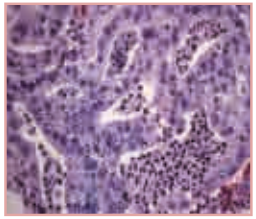
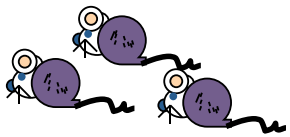
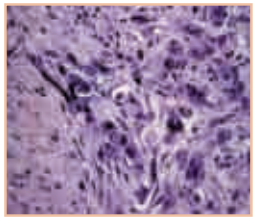
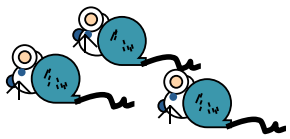


Biobanks make the development of drugs and diagnostic tools more efficient

- Individualised Molecular Pancreatic Cancer Therapy (IMPACT) trial
  - APGI patients with targets that are ready for “Prime Time”
  - Primary Xenografts and cell lines generated from APGI patients for others



Biobank of patient tumorgrafts to associate genetic profiles to drug response

Patient cancer	Genetic profile	Patient Xenografts	Genetic profile	Drug response
	II		II	A
	III		III	B
	IV		IV	C

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