University of Glasgow | College of Medical, Veterinary & Life Sciences

Molecular Phenotype Guided Therapy for Pancreatic Cancer

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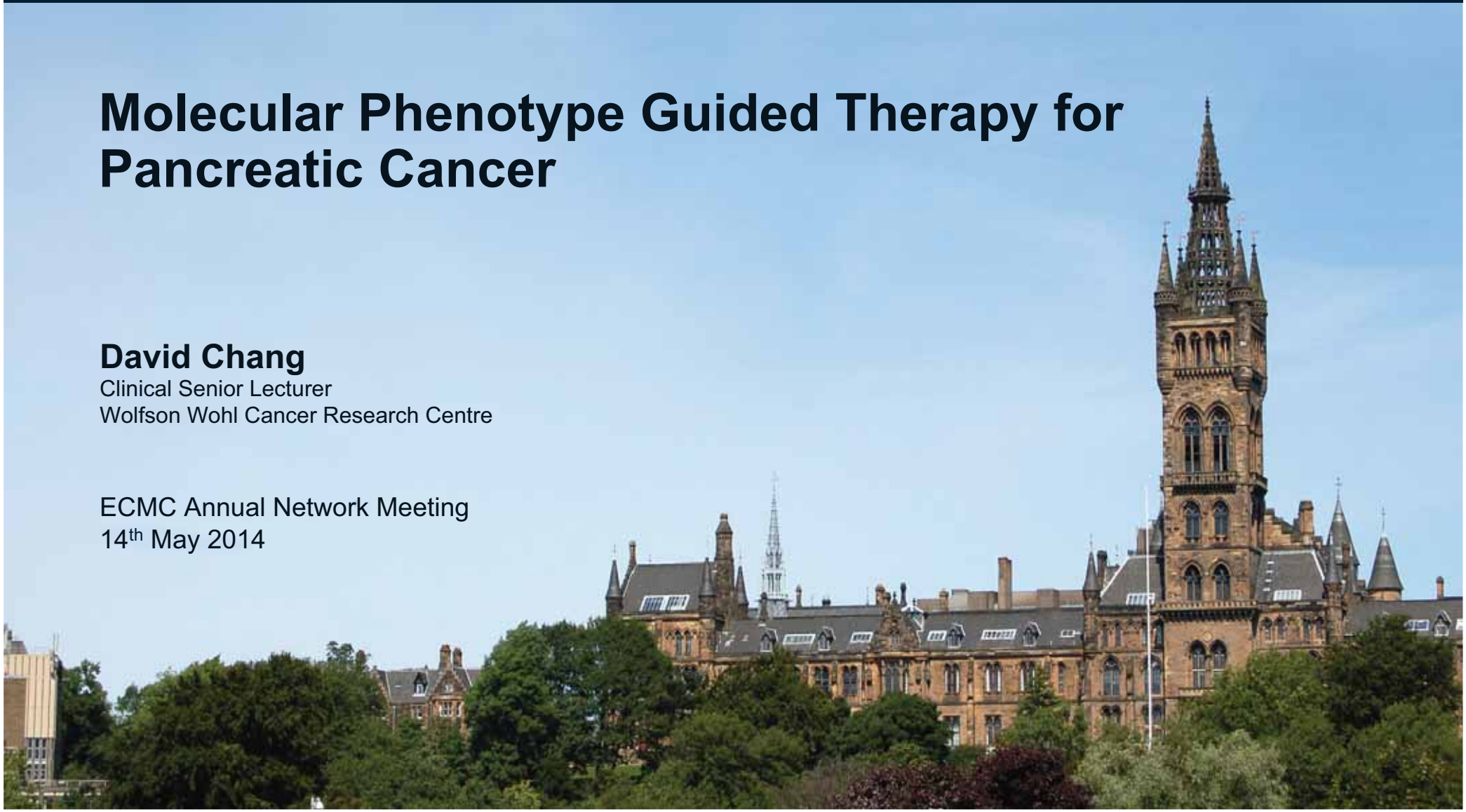
ECMC Annual Network Meeting
14th May 2014



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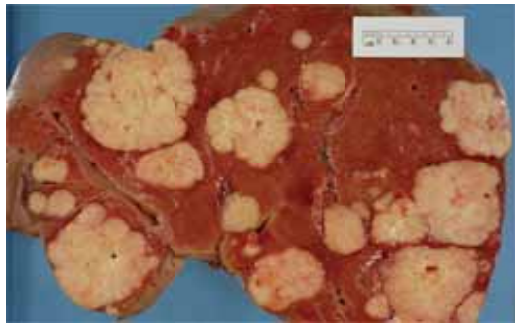
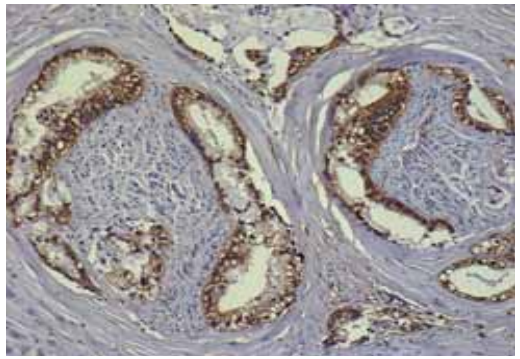
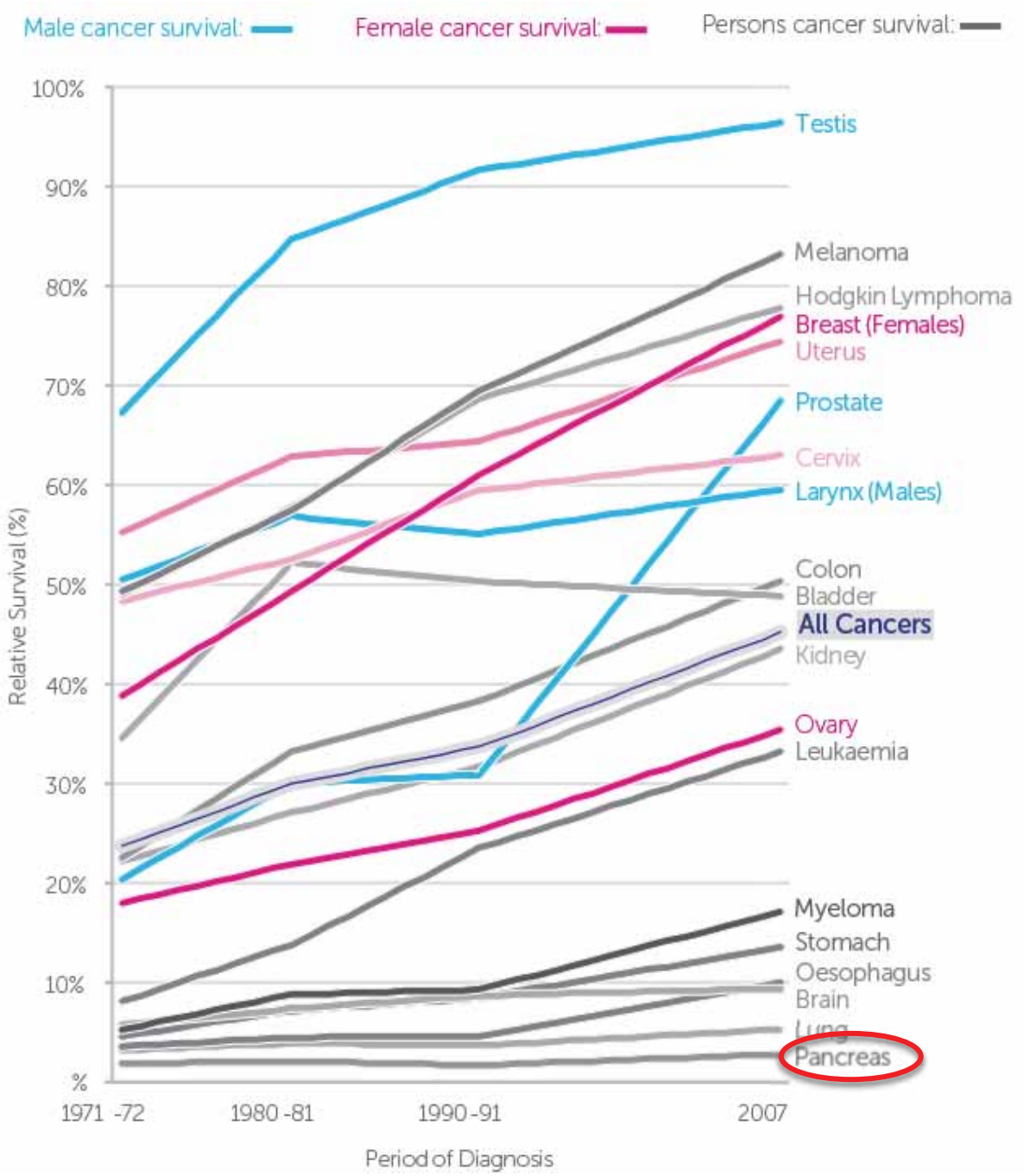
Outline

- Cancer is heterogeneous
  - APGI sequencing project (mutational landscape)
  - Therapeutic implications
  - DNA-damaging agents responsive phenotype

- Lesson learnt so far and challenges ahead






Male cancer survival:
Female cancer survival:
Persons cancer survival:
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
%
Relative Survival (%)
1971 -72
1980 -81
1990 -91
2007
Period of Diagnosis
Testis
Melanoma
Hodgkin Lymphoma
Breast (Females)
Uterus
Prostate
Cervix
Larynx (Males)
Colon
Bladder
All Cancers
Kidney
Ovary
Leukaemia
Myeloma
Stomach
Oesophagus
Brain
Lung
Pancreas

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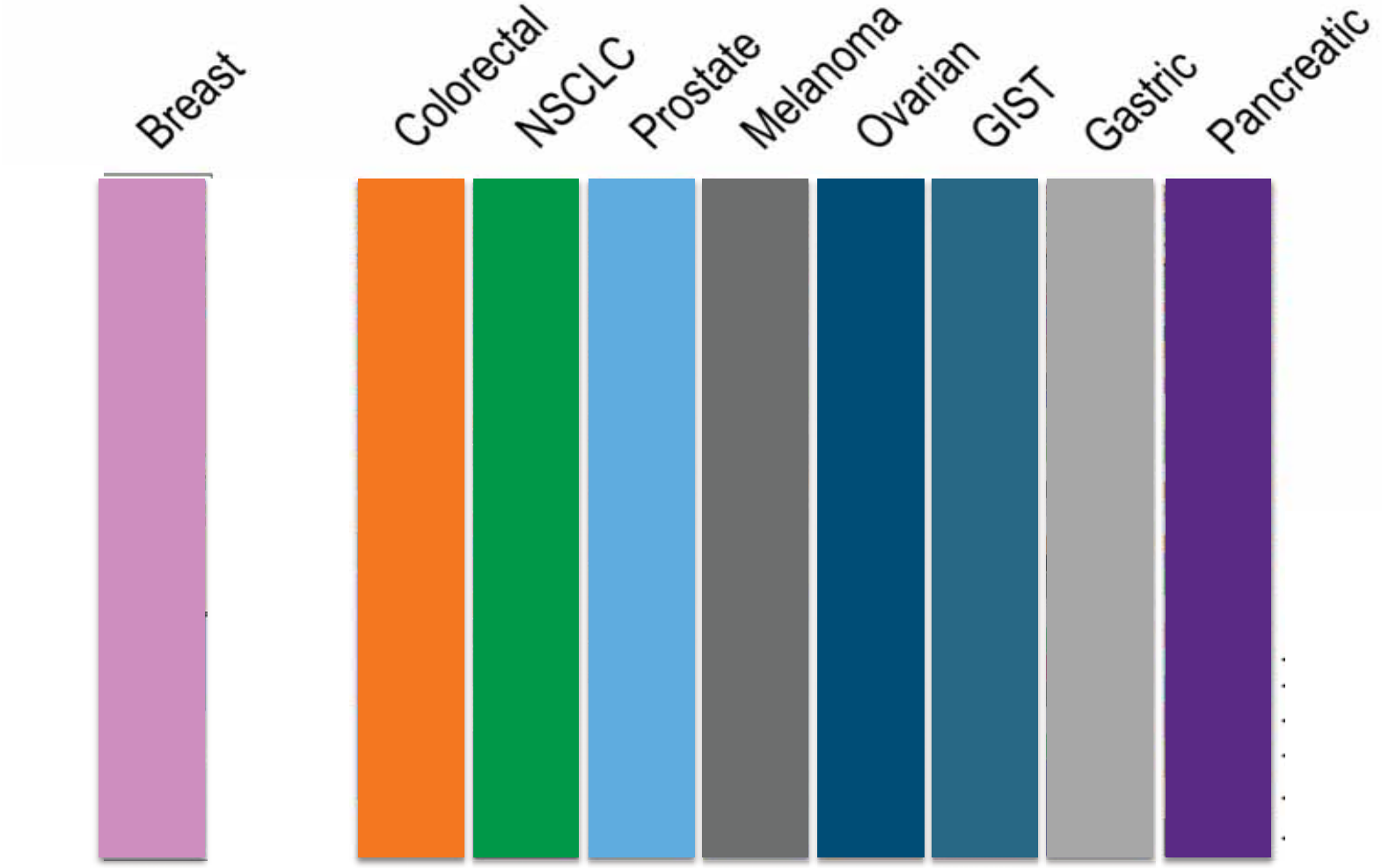
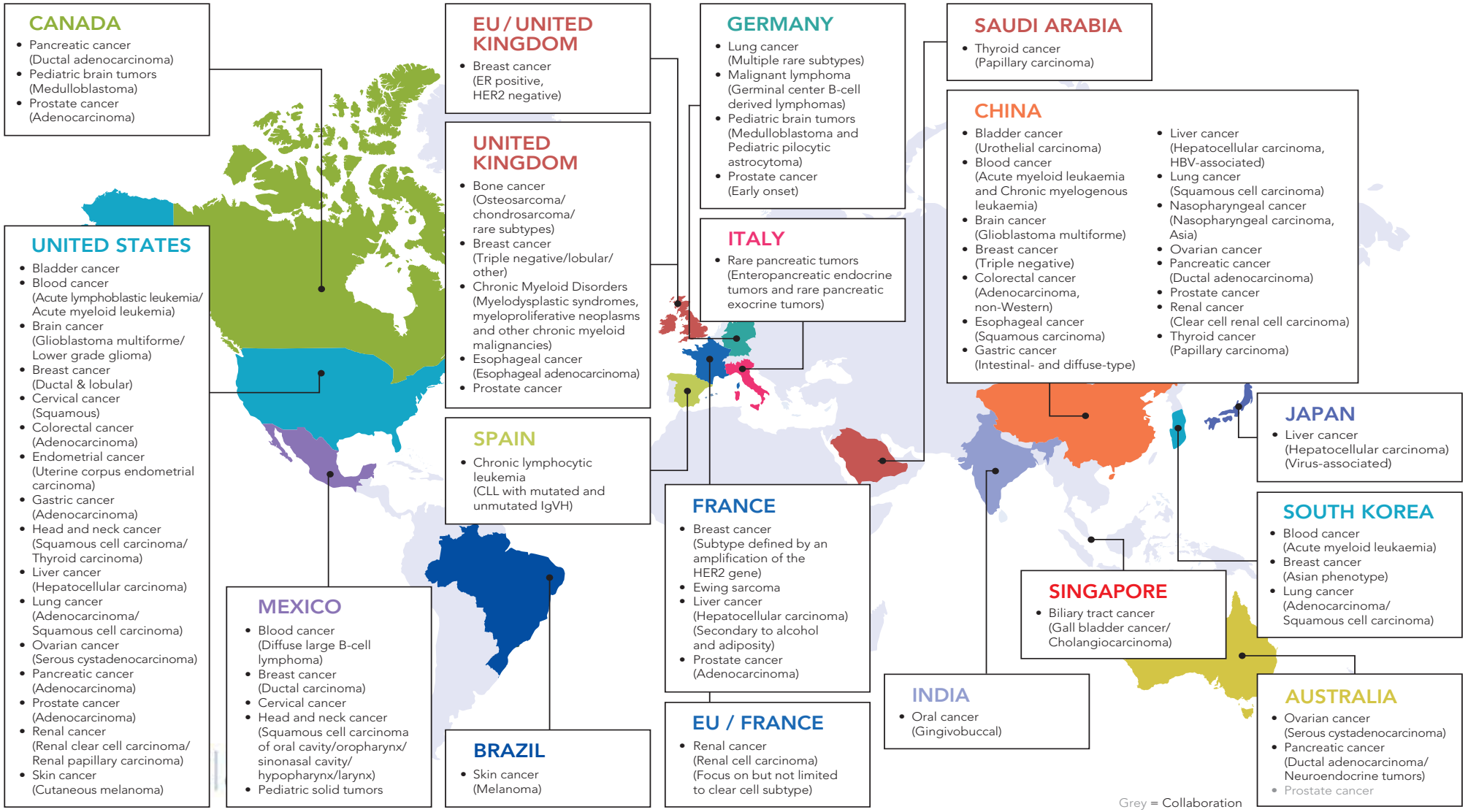
Cancer is complex & Heterogeneous



International Cancer Genome Consortium (ICGC)

International Cancer Genome Consortium



CANADA
- Pancreatic cancer (Ductal adenocarcinoma)
- Pediatric brain tumors (Medulloblastoma)
- Prostate cancer (Adenocarcinoma)

UNITED STATES
- Bladder cancer
- Blood cancer (Acute lymphoblastic leukemia/ Acute myeloid leukemia)
- Brain cancer (Glioblastoma multiforme/ Lower grade glioma)
- Breast cancer (Ductal & lobular)
- Cervical cancer (Squamous)
- Colorectal cancer (Adenocarcinoma)
- Endometrial cancer (Uterine corpus endometrial carcinoma)
- Gastric cancer (Adenocarcinoma)
- Head and neck cancer (Squamous cell carcinoma/ Thyroid carcinoma)
- Liver cancer (Hepatocellular carcinoma)
- Lung cancer (Adenocarcinoma/ Squamous cell carcinoma)
- Ovarian cancer (Serous cystadenocarcinoma)
- Pancreatic cancer (Adenocarcinoma)
- Prostate cancer (Adenocarcinoma)
- Renal cancer (Renal clear cell carcinoma/ Renal papillary carcinoma)
- Skin cancer (Cutaneous melanoma)

MEXICO
- Blood cancer (Diffuse large B-cell lymphoma)
- Breast cancer (Ductal carcinoma)
- Cervical cancer
- Head and neck cancer (Squamous cell carcinoma of oral cavity/oropharynx/ sinonasal cavity/ hypopharynx/larynx)
- Pediatric solid tumors

BRAZIL
- Skin cancer (Melanoma)

EU / UNITED KINGDOM
- Breast cancer (ER positive, HER2 negative)

UNITED KINGDOM
- Bone cancer (Osteosarcoma/ chondrosarcoma/ rare subtypes)
- Breast cancer (Triple negative/lobular/ other)
- Chronic Myeloid Disorders (Myelodysplastic syndromes, myeloproliferative neoplasms and other chronic myeloid malignancies)
- Esophageal cancer (Esophageal adenocarcinoma)
- Prostate cancer

SPAIN
- Chronic lymphocytic leukemia (CLL with mutated and unmutated IgVH)

GERMANY
- Lung cancer (Multiple rare subtypes)
- Malignant lymphoma (Germinal center B-cell derived lymphomas)
- Pediatric brain tumors (Medulloblastoma and Pediatric pilocytic astrocytoma)
- Prostate cancer (Early onset)

ITALY
- Rare pancreatic tumors (Enteropancreatic endocrine tumors and rare pancreatic exocrine tumors)

FRANCE
- Breast cancer (Subtype defined by an amplification of the HER2 gene)
- Ewing sarcoma
- Liver cancer (Hepatocellular carcinoma) (Secondary to alcohol and adiposity)
- Prostate cancer (Adenocarcinoma)

EU / FRANCE
- Renal cancer (Renal cell carcinoma) (Focus on but not limited to clear cell subtype)

SAUDI ARABIA
- Thyroid cancer (Papillary carcinoma)

CHINA
- Bladder cancer (Urothelial carcinoma)
- Blood cancer (Acute myeloid leukaemia and Chronic myelogenous leukaemia)
- Brain cancer (Glioblastoma multiforme)
- Breast cancer (Triple negative)
- Colorectal cancer (Adenocarcinoma, non-Western)
- Esophageal cancer (Squamous carcinoma)
- Gastric cancer (Intestinal- and diffuse-type)
- Liver cancer (Hepatocellular carcinoma, HBV-associated)
- Lung cancer (Squamous cell carcinoma)
- Nasopharyngeal cancer (Nasopharyngeal carcinoma, Asia)
- Ovarian cancer
- Pancreatic cancer (Ductal adenocarcinoma)
- Prostate cancer
- Renal cancer (Clear cell renal cell carcinoma)
- Thyroid cancer (Papillary carcinoma)

JAPAN
- Liver cancer (Hepatocellular carcinoma) (Virus-associated)

SOUTH KOREA
- Blood cancer (Acute myeloid leukaemia)
- Breast cancer (Asian phenotype)
- Lung cancer (Adenocarcinoma/ Squamous cell carcinoma)

SINGAPORE
- Biliary tract cancer (Gall bladder cancer/ Cholangiocarcinoma)

INDIA
- Oral cancer (Gingivobuccal)

AUSTRALIA
- Ovarian cancer (Serous cystadenocarcinoma)
- Pancreatic cancer (Ductal adenocarcinoma/ Neuroendocrine tumors)
- Prostate cancer

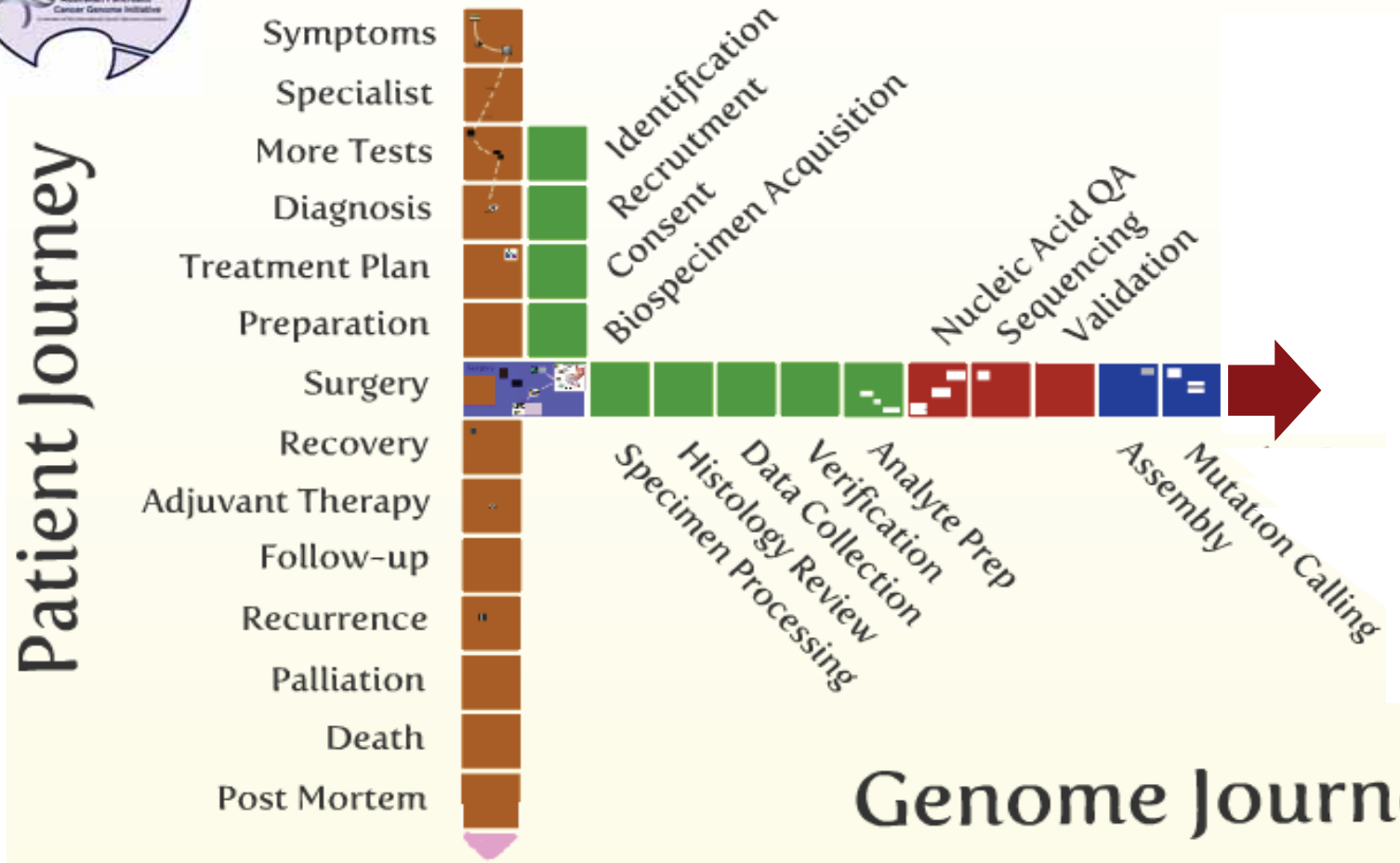
Grey = Collaboration

Australian Pancreatic Cancer Genome Initiative (APGI)

Prospective observational cohort study design (350 PDAC)


Biankin

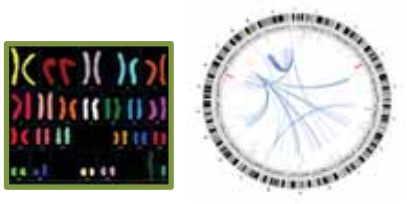

Grimmond

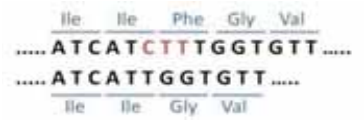


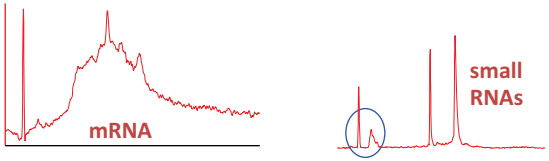
ICGC Data Portal
"ICGCMart"

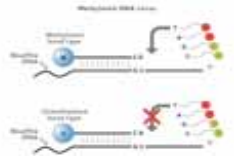
Data Generation strategy:

Queensland Centre for MEDICAL GENOMICS





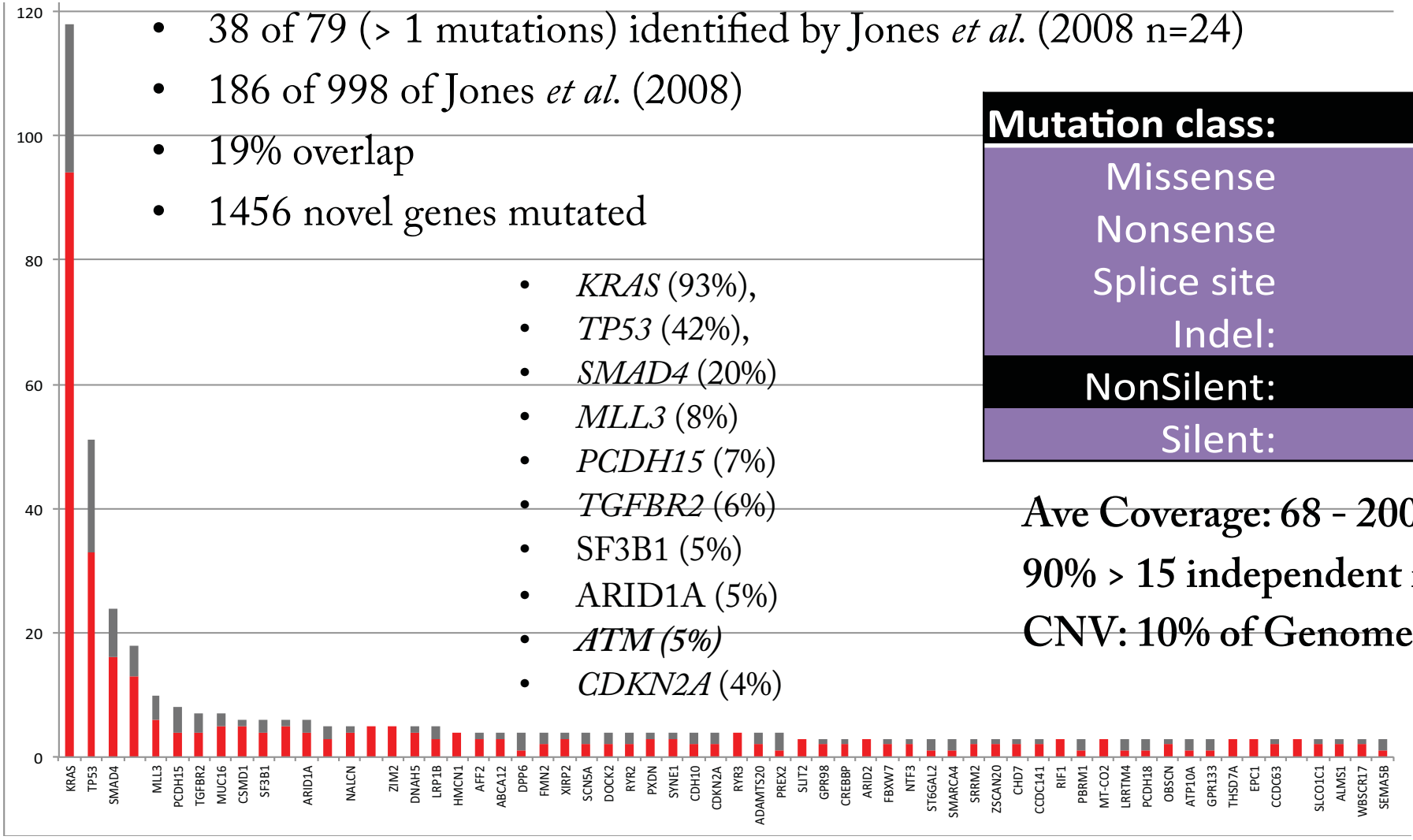




Genome	Exome	Transcriptome	Epigenome
			
SNP/CNV Chip analysis, gDNA sequencing **40-100% Cellularity**	Exome sequencing **>20% cellularity**	Expression array, mRNAseq, miRNAseq	Methyl Miner enrichment, methyl seq
Tumor & normal 40x /80x fold	Tumor & normal >95% 20x ~250x	Tumor tissue & adjacent normal ~100 million reads	Tumor & adjacent normal : 450K array

Genomic Landscape of PDAC

- **Whole Exome Capture and Sequencing + CNV (n=142)**
  (Biankin et al., *Nature* 2012)
- 38 of 79 (> 1 mutations) identified by Jones *et al.* (2008 n=24)
- 186 of 998 of Jones *et al.* (2008)
- 19% overlap
- 1456 novel genes mutated



- *KRAS* (93%),
- *TP53* (42%),
- *SMAD4* (20%)
- *MLL3* (8%)
- *PCDH15* (7%)
- *TGFBR2* (6%)
- SF3B1 (5%)
- ARID1A (5%)
- *ATM (5%)*
- *CDKN2A* (4%)

Mutation class:	Total:
Missense	1684
Nonsense	99
Splice site	89
Indel:	144
NonSilent:	2016
Silent:	611

Ave Coverage: 68 - 200x

90% > 15 independent reads

CNV: 10% of Genome

Non-Silent Point Mutations in PDAC (WGS)

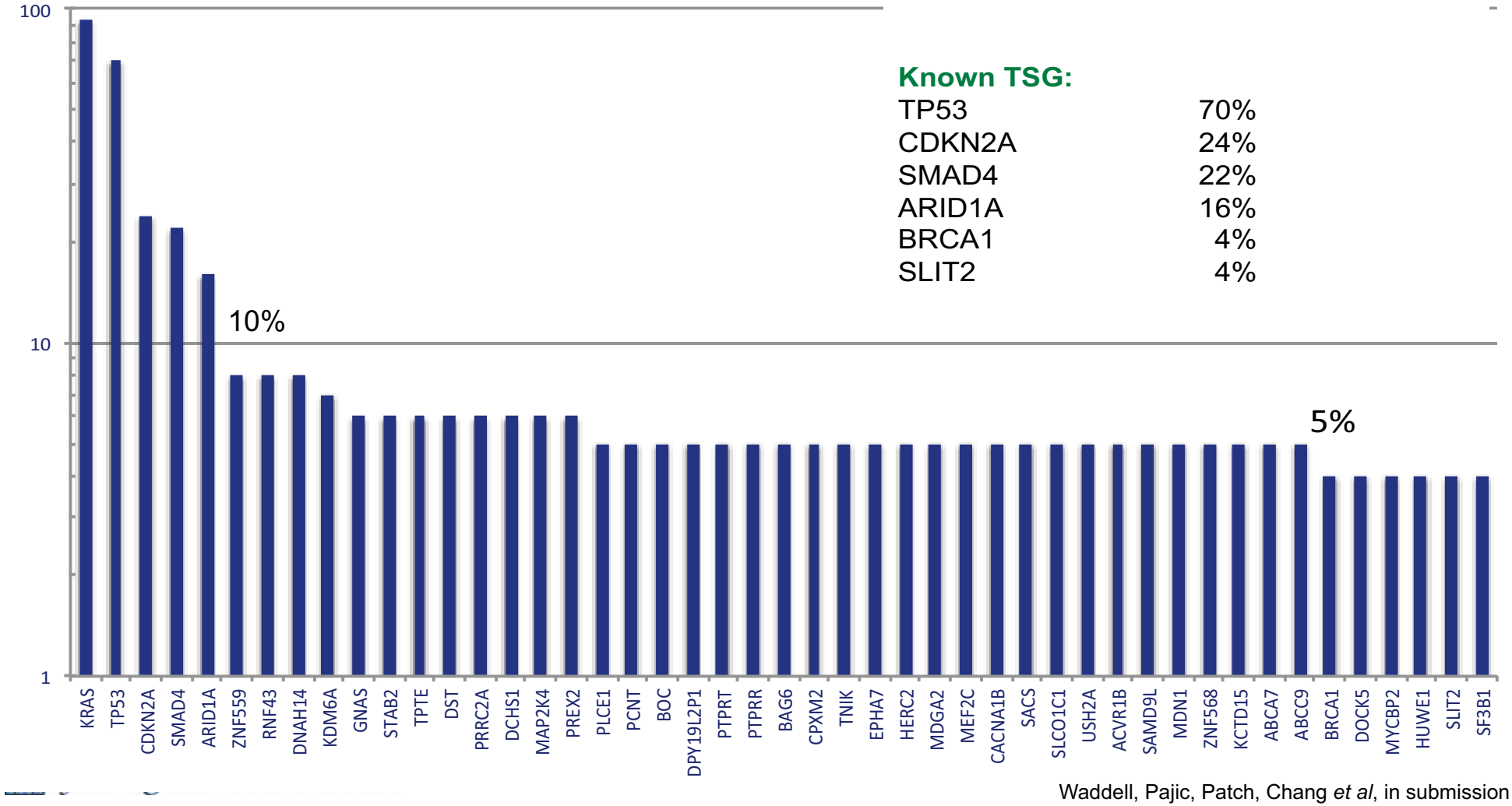
Queensland Centre for MEDICAL GENOMICS

Known oncogenes:

KRAS:	93%
GNAS:	7%
SF3B1:	4%

Known TSG:

TP53	70%
CDKN2A	24%
SMAD4	22%
ARID1A	16%
BRCA1	4%
SLIT2	4%



Waddell, Pajic, Patch, Chang *et al*, in submission

Heterogeneity = Therapeutic development implications

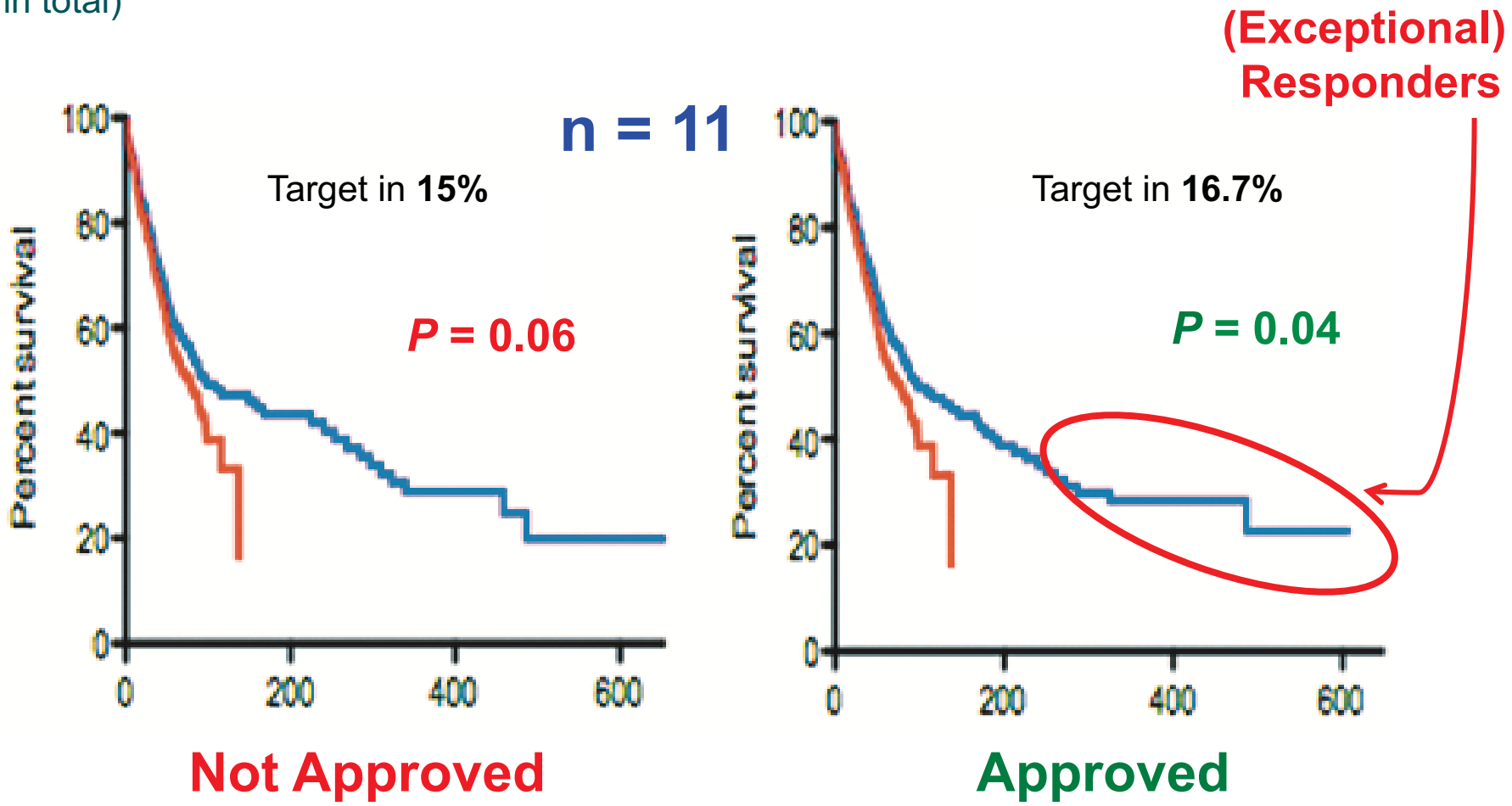
The Second Rule of Clinical Trials:

"It (the drug) must be used on a simple, not a composite, disease."

Avicenna, The Canon of Medicine, 1025AD

Fool's Gold or Lost Treasures??

Simulation of 334 NSCLC patients (actual survival) in each arm (668 in total)



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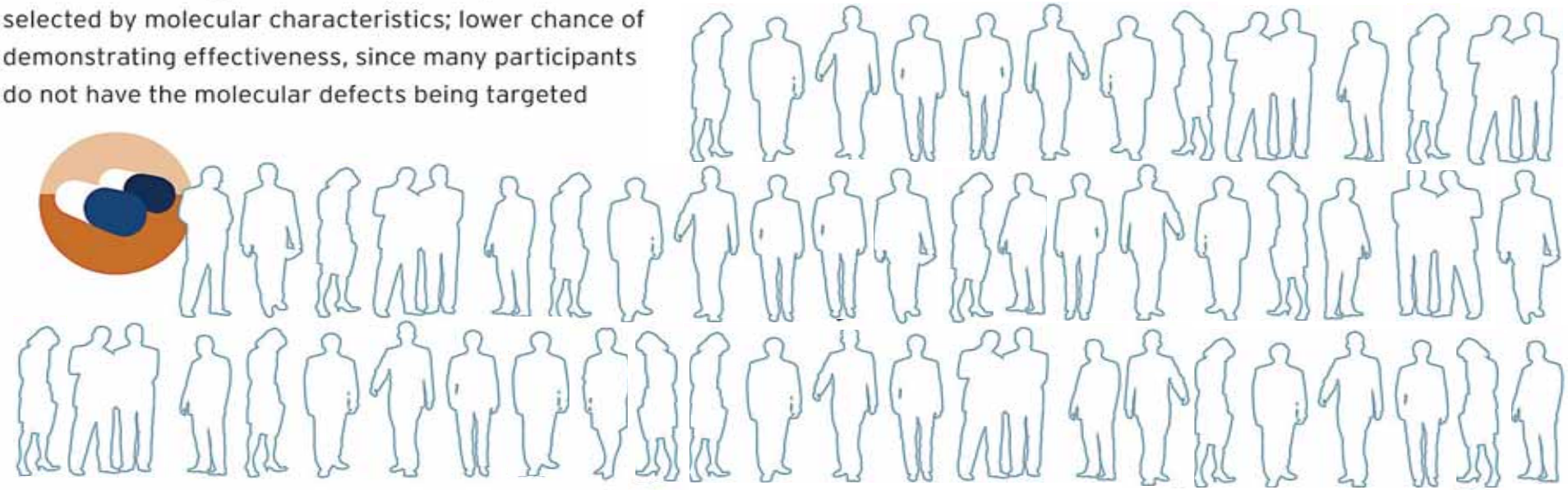
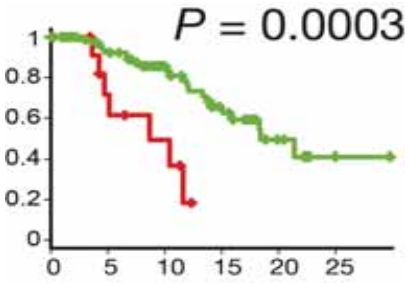
Stewart & Kurzrock, *BMC Cancer* 2013

Smaller Trials, Greater Chance of Success

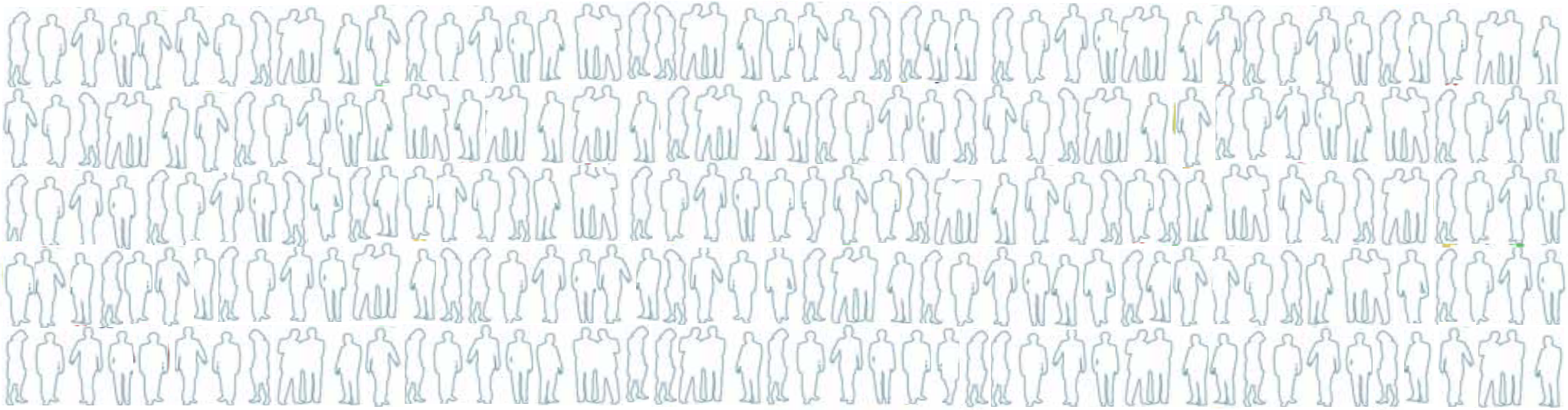
OLD MODEL: Large numbers of patients, not selected by molecular characteristics; lower chance of demonstrating effectiveness, since many participants do not have the molecular defects being targeted



NEW MODEL: Small patient populations, all with the relevant mutations or genetic defects; greater chance of desired results, since all participants have the potential to respond



Personalising Cancer Care



Test each person to choose the right treatment

Trial of Drug A

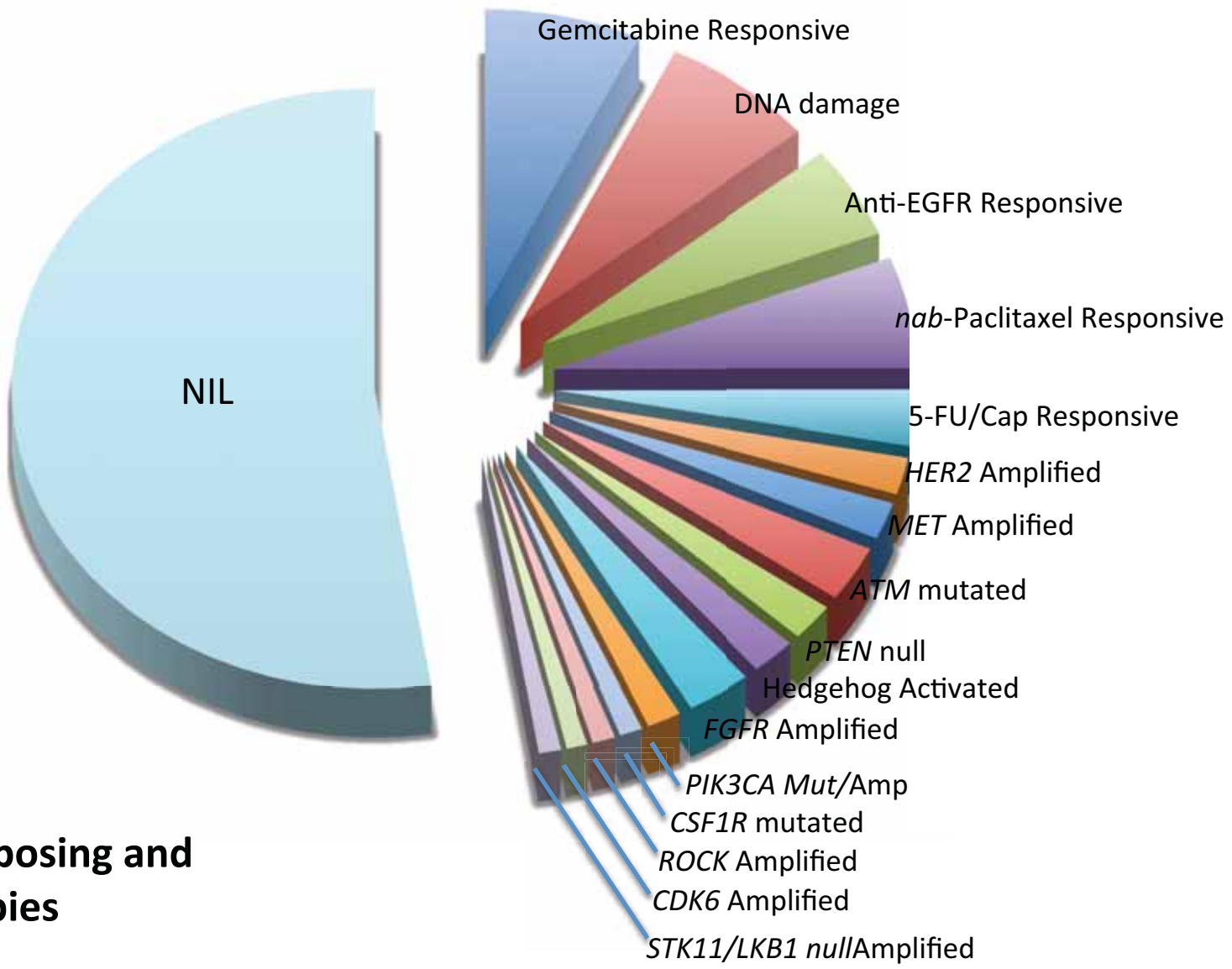
Trial of Drug B

Trial of Drug C

Trial of Drug D

New Targets and Drugs

Actionable Phenotypes in Pancreatic Cancer

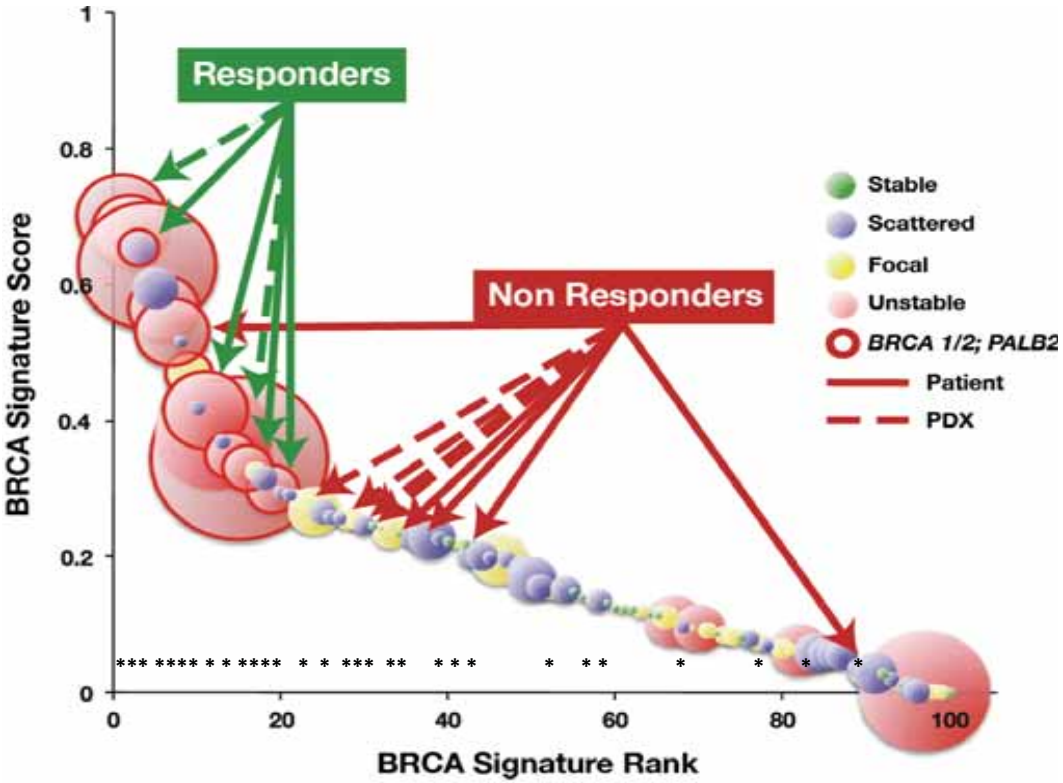


Rescuing, Repurposing and Emerging Therapies

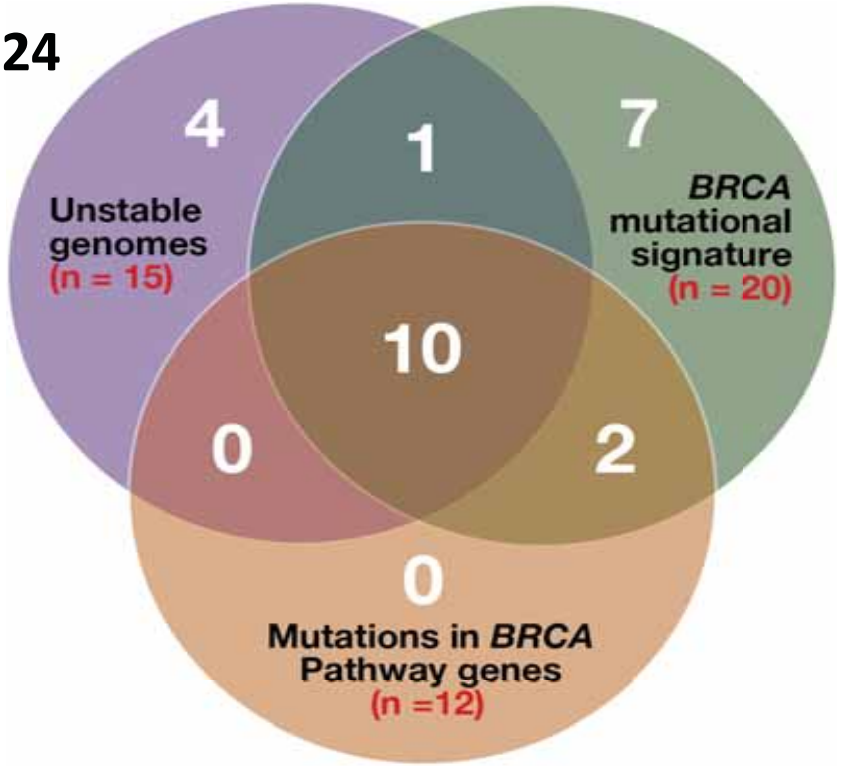
Approach

- N = 100 WGS
- Phenotype-to-genotype analysis

- DNA-damaging agent responsive phenotype is potentially substantially larger than previously believed.



N = 24



- Platinum responders are enriched by high *BRCA* signature ranking with overlapping unstable genomes and mutations in *BRCA* DNA maintenance pathway genes

Waddell, Pajic, Patch, Chang *et al*, in submission

Studying Exceptional Responders

nature REVIEWS CANCER

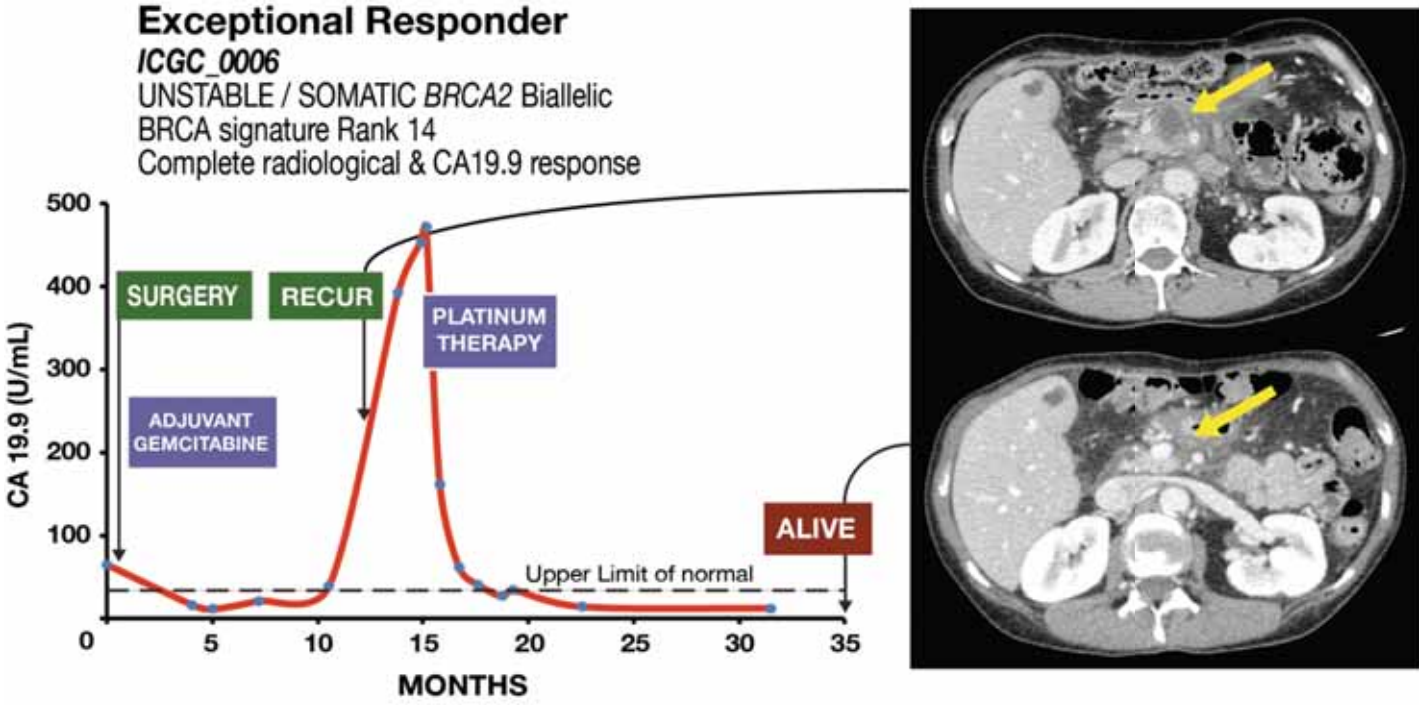
CLINICAL INSIGHTS

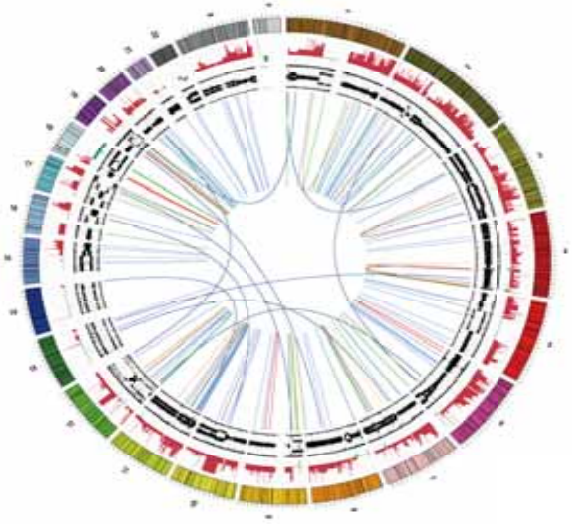
Mining the genomes of exceptional responders

David K. Chang[1–5], Sean M. Grimmond[1,6], T. R. Jeffry Evans[1] and Andrew V. Biankin[1–5]

Abstract | The National Cancer Institute of the United States recently announced a major new initiative in understanding the genomes or, more broadly, the molecular phenotypes of exceptional responders. What can we expect to learn from exceptional responders? What are the potential benefits, and how do we approach studying them?

Chang et al, *Nat Rev Cancer,* 2014





Pajic & Chang et al, in preparation

Targeting Actionable Molecular Phenotypes

Initially direct recruitment of ICGC patients
Then panel-based screening

IMPaCT Clinical Trial

Individualised **M**olecular **Pa**ncreatic **C**ancer **T**herapy

Patients are screened for actionable mutations, recruited and randomised between standard therapyand a biomarker driven "Individualised" strategy which evolves and adapts as new information comes to light.

***HER2* Amplified (2%): GEM + Trastuzumab**
***KRAS* wild type (5%): GEM + Erlotinib**
***BRCA2* Germ Line mutant (3%): MMC + Capecitabine**

Lessons Learnt (@#$% !)

- Logistically demanding: tissue acquisition, QC, drugs
- Patients randomised to standard of care withdraw and buy drug themselves
- Screening time (main problem is sample delivery)
- Sample variability (different path labs)
- Low prevalence phenotypes (need to screen large numbers)
- Screening cost (genome maybe cheaper, bioinformatics still the same)

Lessons Learnt (@#$% !)

- Patients without an actionable phenotype (what is best SOC?)
- Social and ethical implications with sequencing (framework for return of results)
- Change of technology (re-validation)
- Lots more to be learnt & lots more challenges ahead

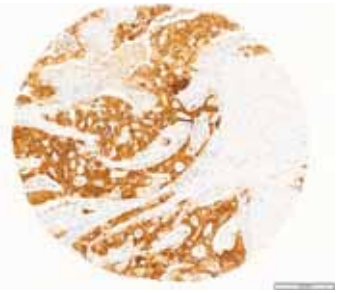
Biobanking & QC

APGI

International Cancer Genome Consortium

~ 700 cases

Amber Johns and Team



1. Independent Pathological review in Australia, Italy and USA.

2. 5mm^3 frozen blocks of Tumour are sectioned to locate non-tumour tissue.

GARVAN INSTITUTE

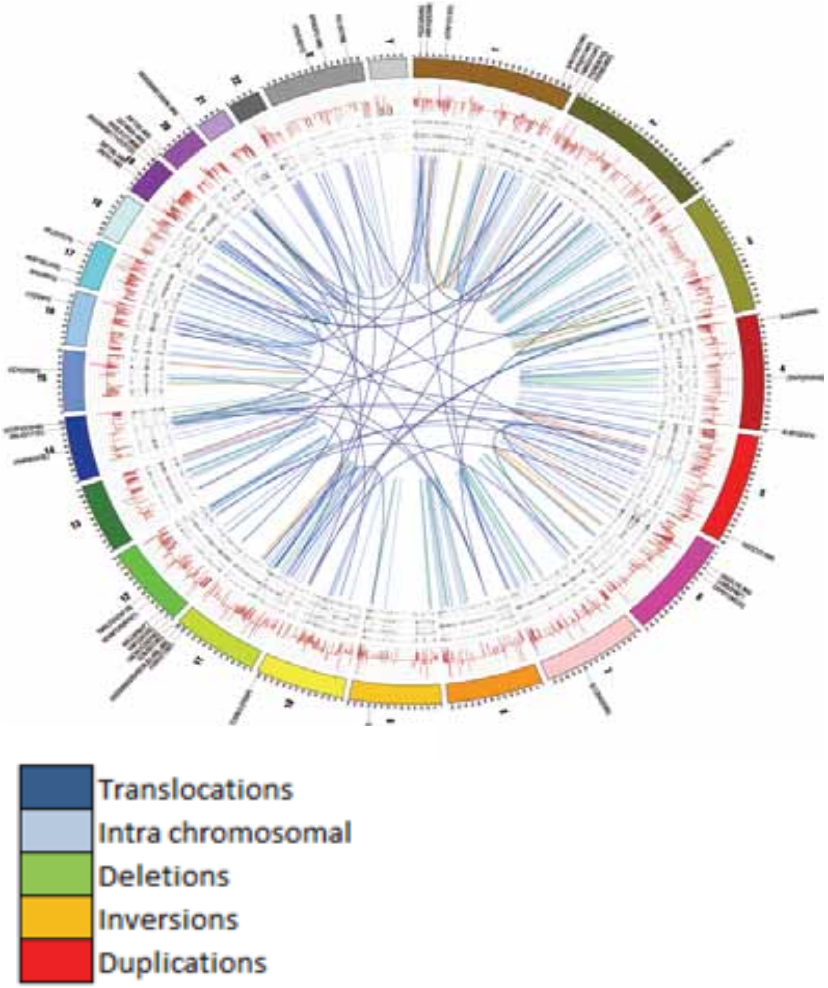
Queensland Centre for MEDICAL GENOMICS

3. Tumour rich regions are dissected form block and DNA/RNA extracted

How to integrate detailed molecular information into clinical practice: Molecular MDT

Patient Cancer Genome Report: APGI-1992

Queensland Centre for MEDICAL GENOMICS



Somatic simple mutations

ABCC9
ADAMTS20
AMAC1L2
B3GALT4
BLID
BRCC3
C3orf62
C11orf94
CACNA1C
CAPN11
CENPE
COLEC11
CTCF
FRMD6
GPR137B
IQCH
KIR3DX1
KLKB1
LEMD2
PIK3CD
PXDN
RPA1
SIGLECP3
SLC26A5
TIMELESS
ZNF432
ZNF132

Genes affected by Inter-chromosomal translocations

FGFR1 (bi-allelic)
LYPD6B
NRXN3
SFTPB
TNPO1
TP53BP2
ZNF468

Genes affected by intra-chromosomal breakpoint

133 genes

Expressed Fusion transcript

ATE1 – KLRAQ1

Differential Methylation & Expression

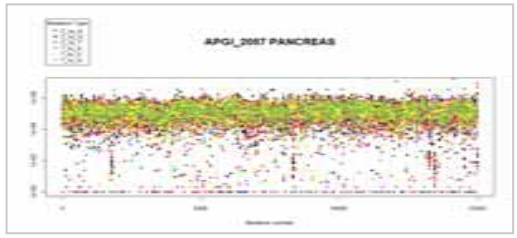
1800 genes

Preclinical models?

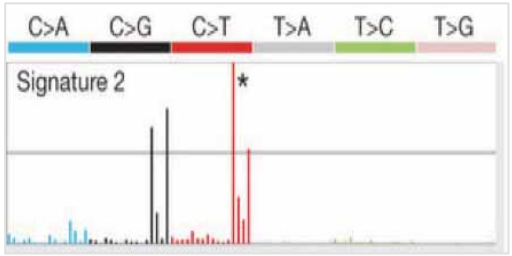
Xenograft
Cell Line

Comprehensive Cancer Genome analysis:

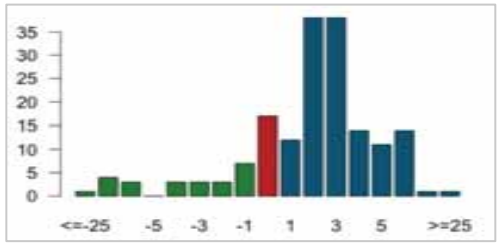
(<3 days)



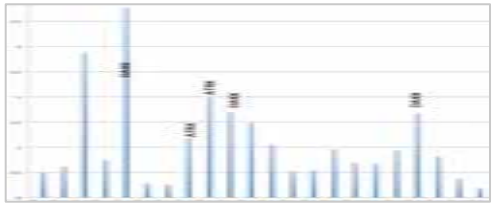
Mutation burden



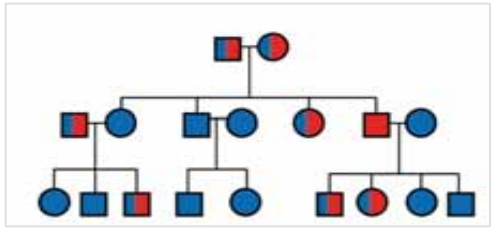
Mutational Signature



Breakpoint Signature



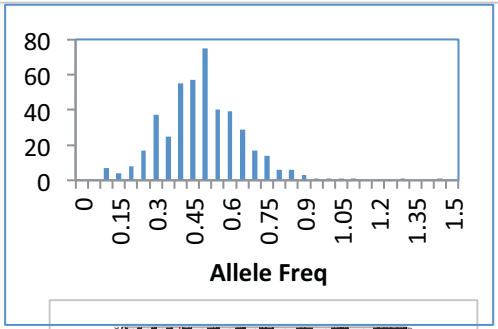
Telomere status

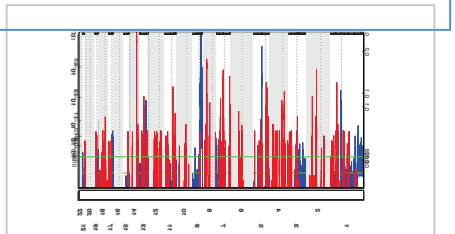


Germline/Inheritance

Mutations

ABCC9,ADAMTS20, AMAC1L2,, BLID, BRCC3, CACNA1C, CAPN11, CENPE, COLEC11, CTCF, FRMD6, GPR137B, LEMD2, PIK3CD, PXDN, RPA1..





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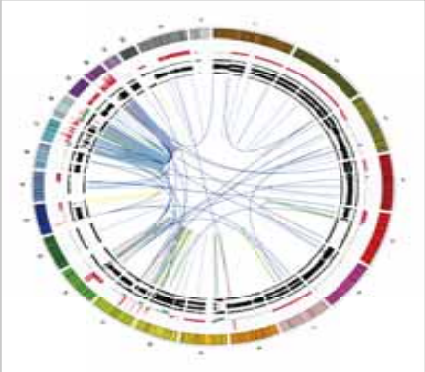
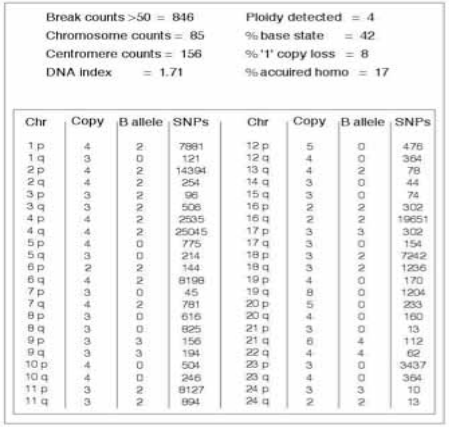
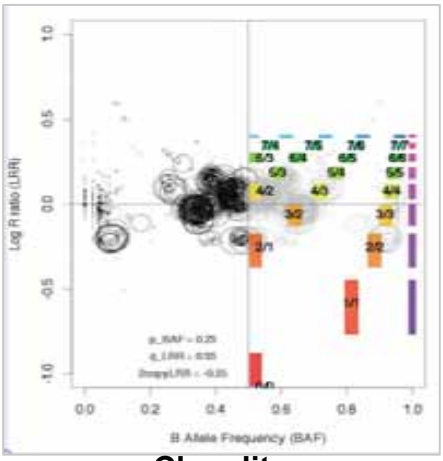


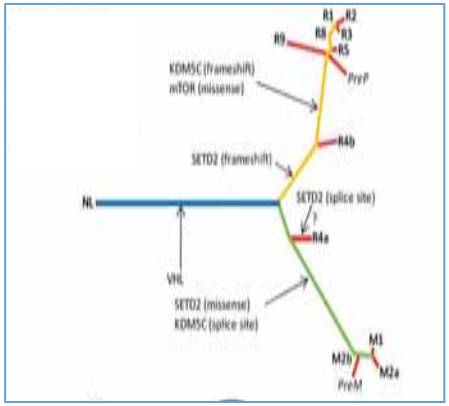
Genome organization



Ploidy



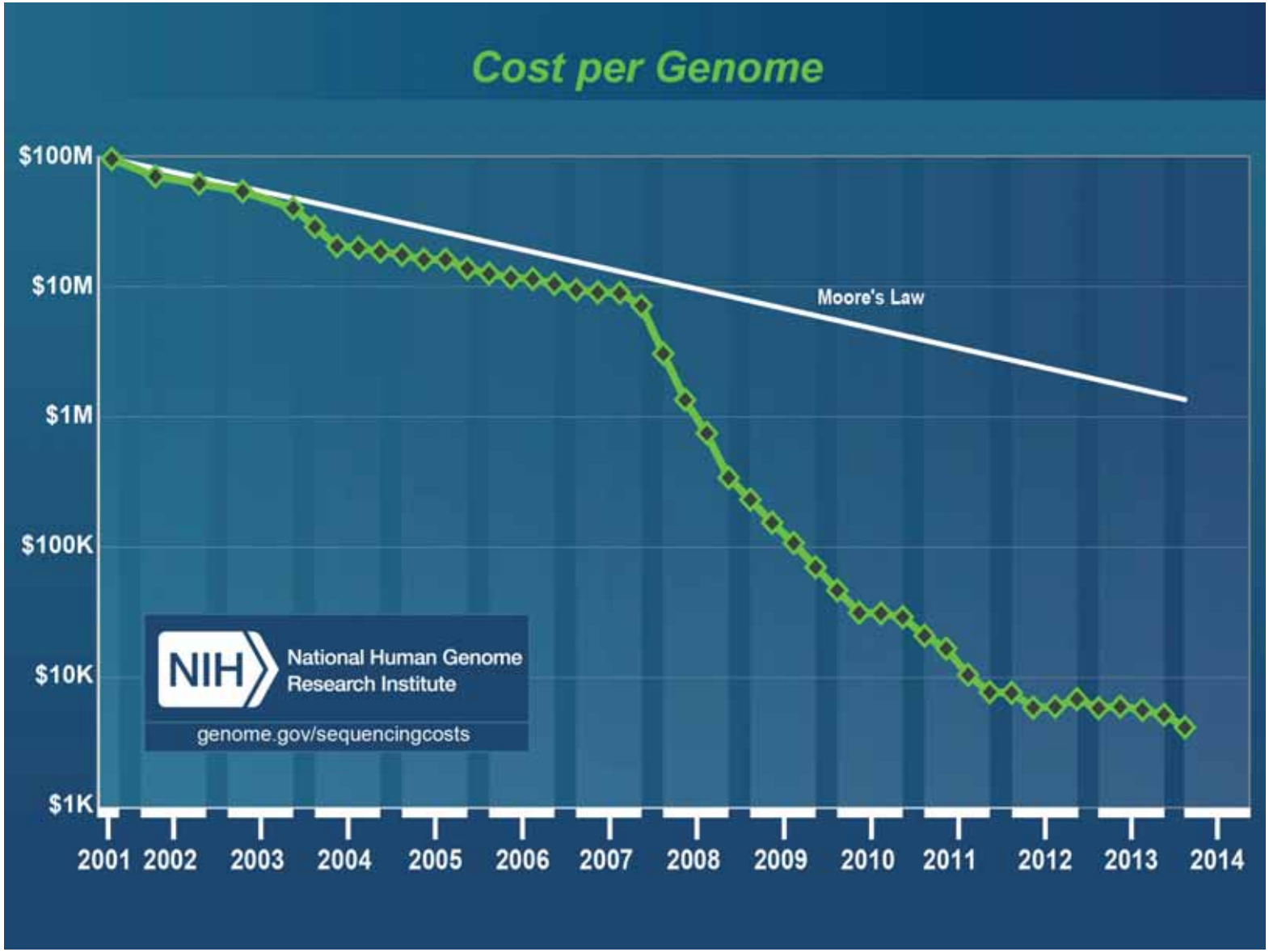
Clonality



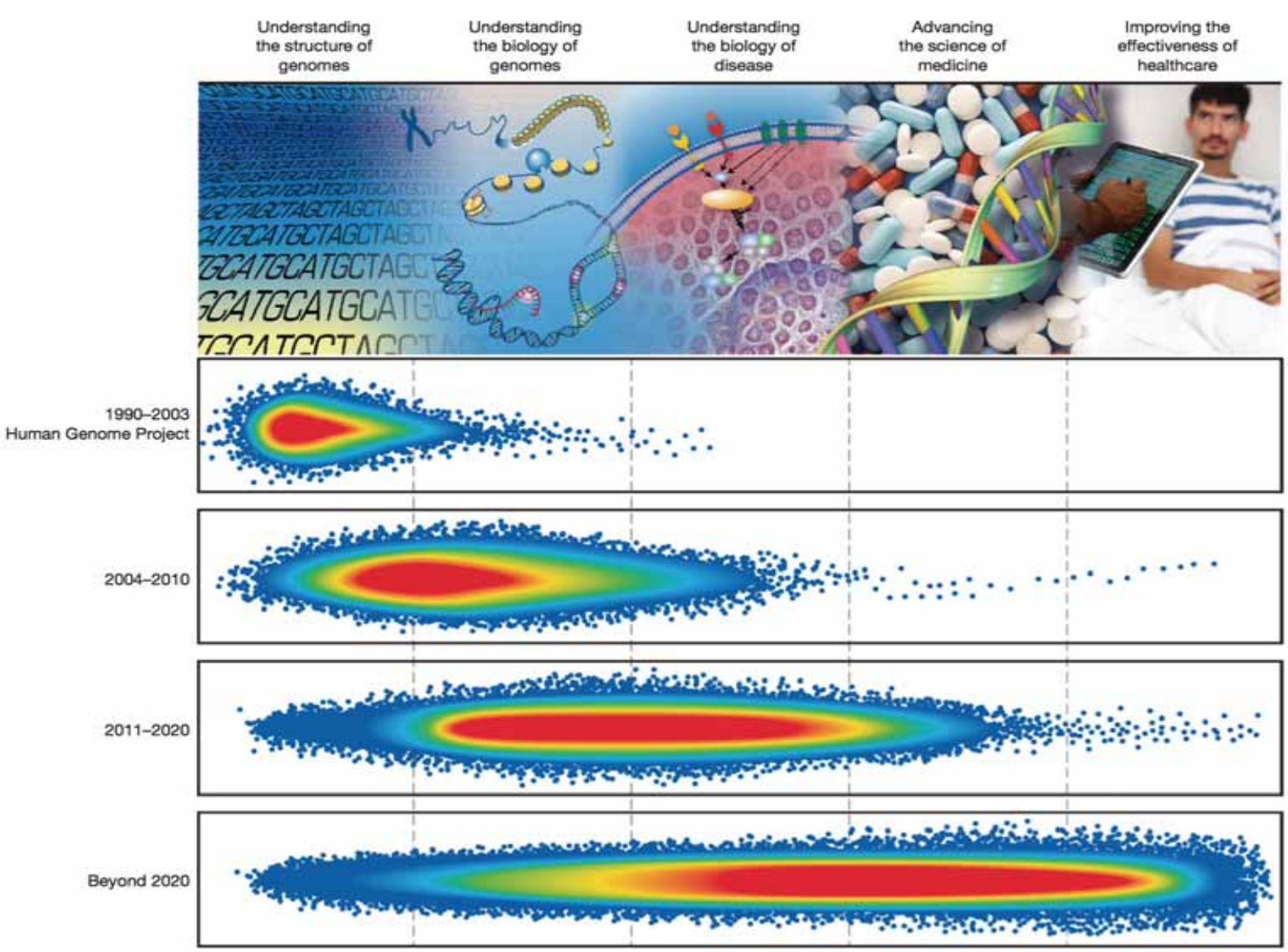
Evolution

Staying ahead of the latest Technology

Cost of Sequencing is dropping dramatically (technology is here!!)

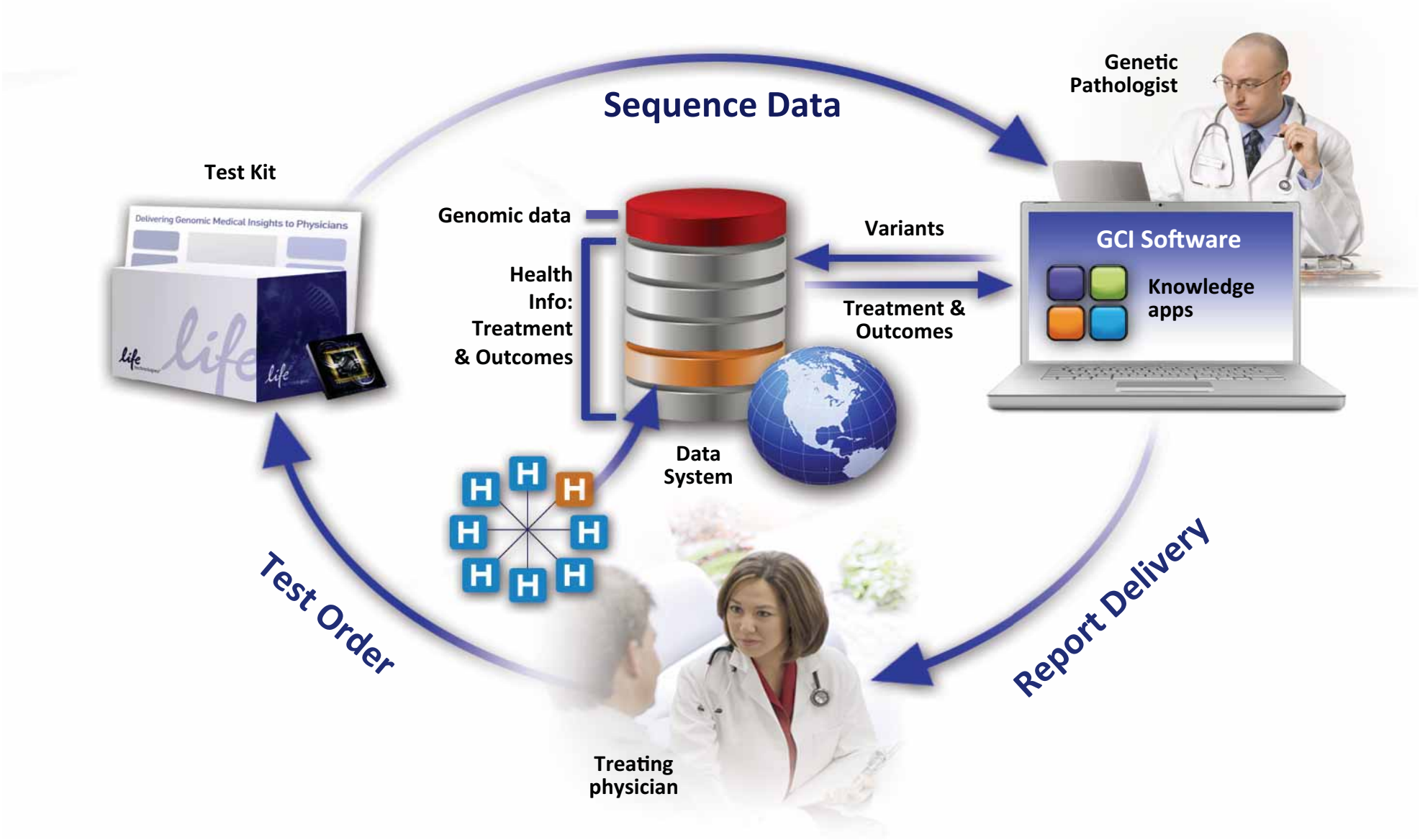


Harness the Technology: From Base Pairs to Bedside

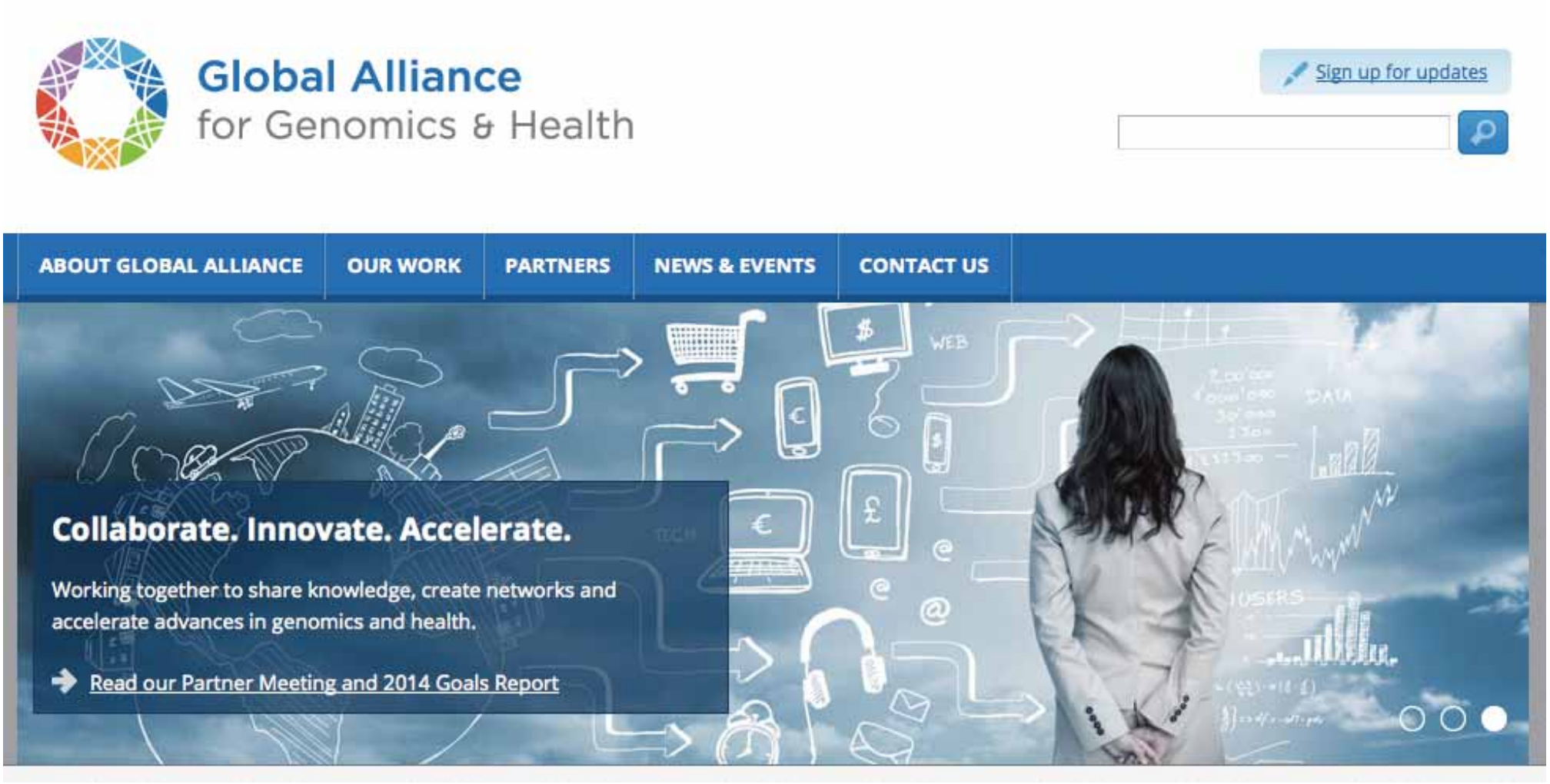


Green & Guyer, *Nature* 2011

Knowledge Bank Approach



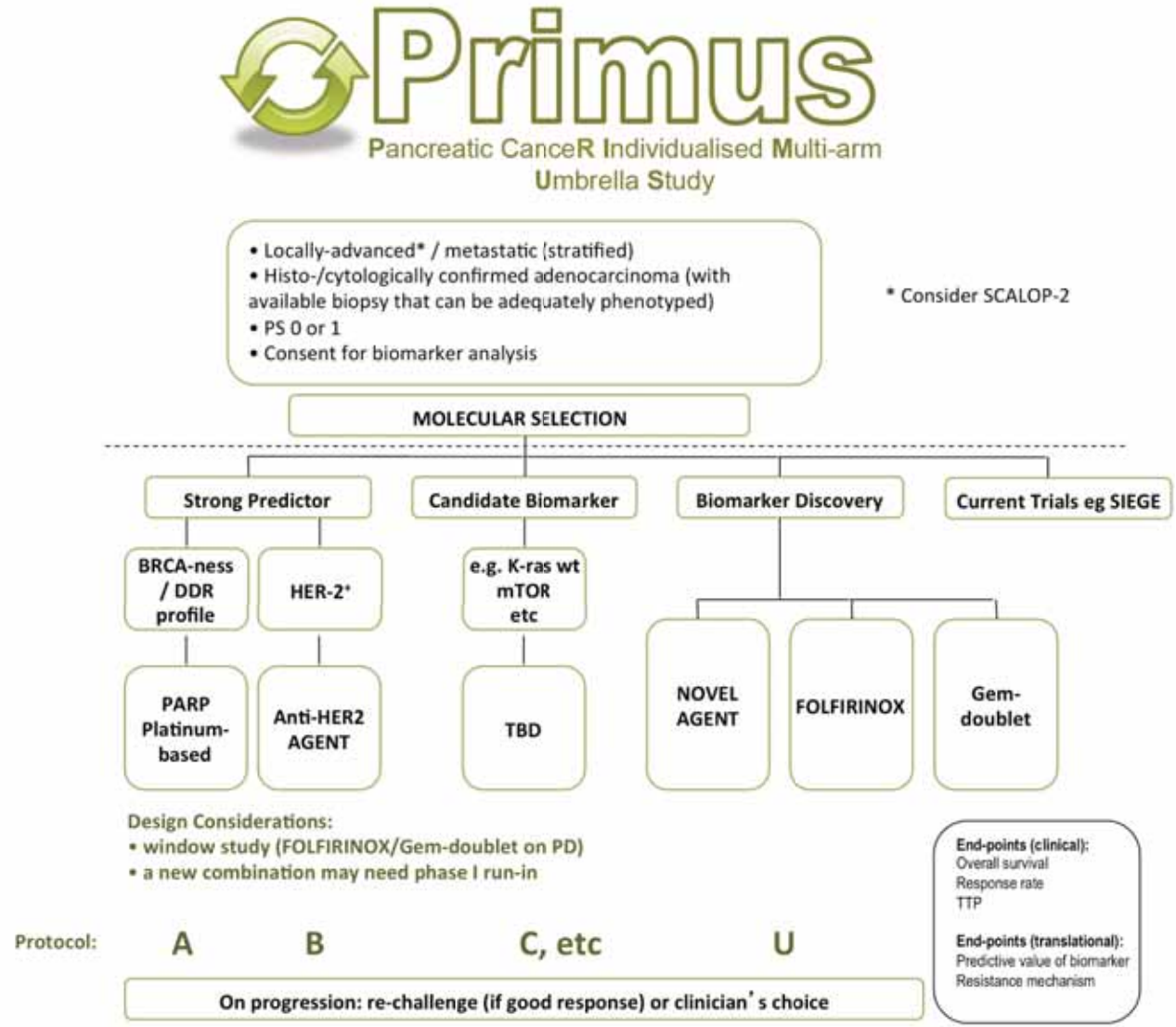
Data Sharing at a Global Scale



http://genomicsandhealth.org/

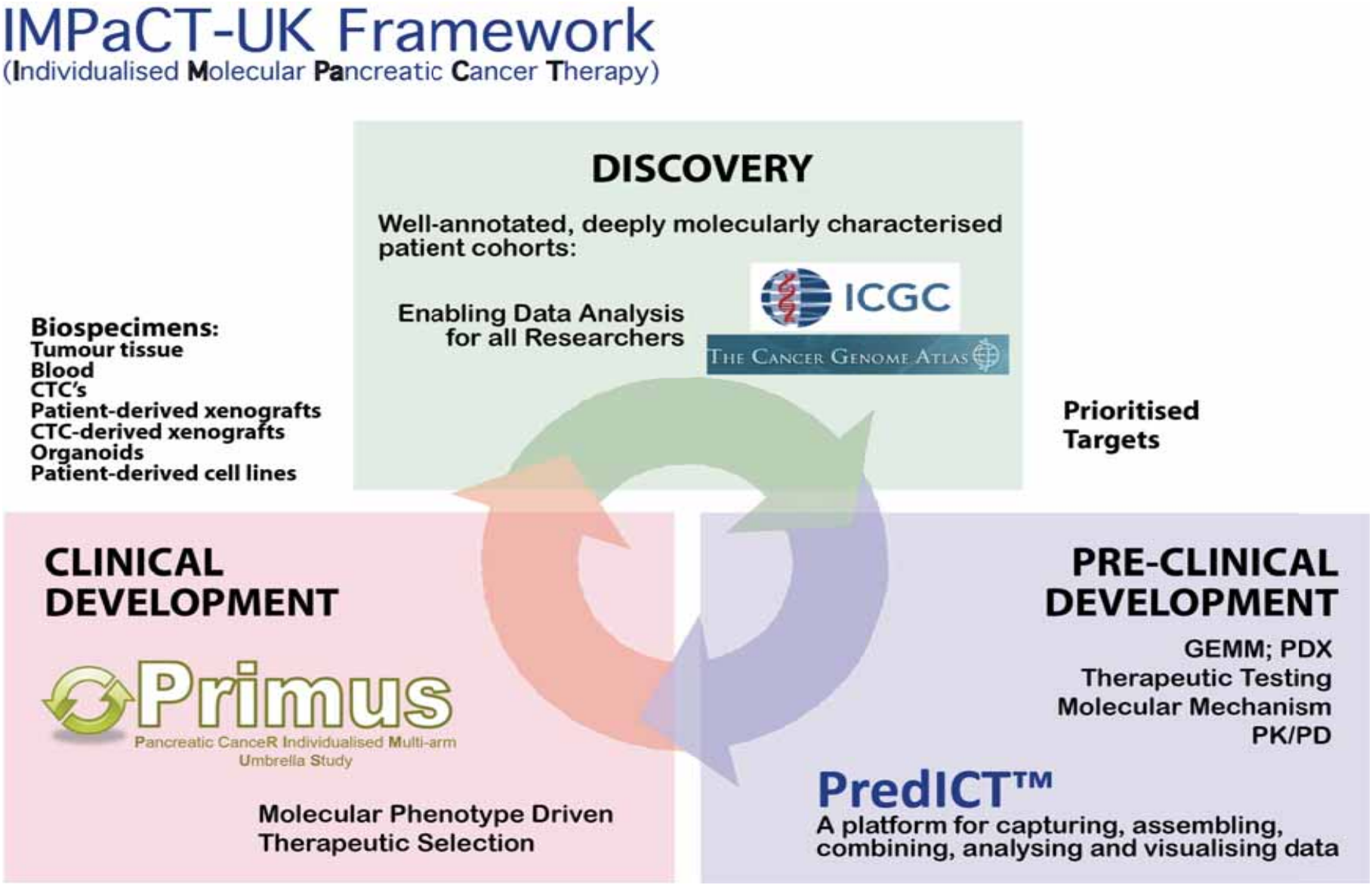
185 organisations, 26 countries
1st meeting March 2014

Smarter and more Nimble Trial Designs



Jeff Evans
Juan Valle
Andrew Biankin
Sean Grimmond
and more……

Better Integration between Key Elements



Translate Research Medicine to Routine Patient Care

- Funding bodies
- Regulatory bodies
- Consumer advocates
- Multiple pharma companies
- Intra-tumoral heterogeniety

- All challenges, but also an unique opportunity

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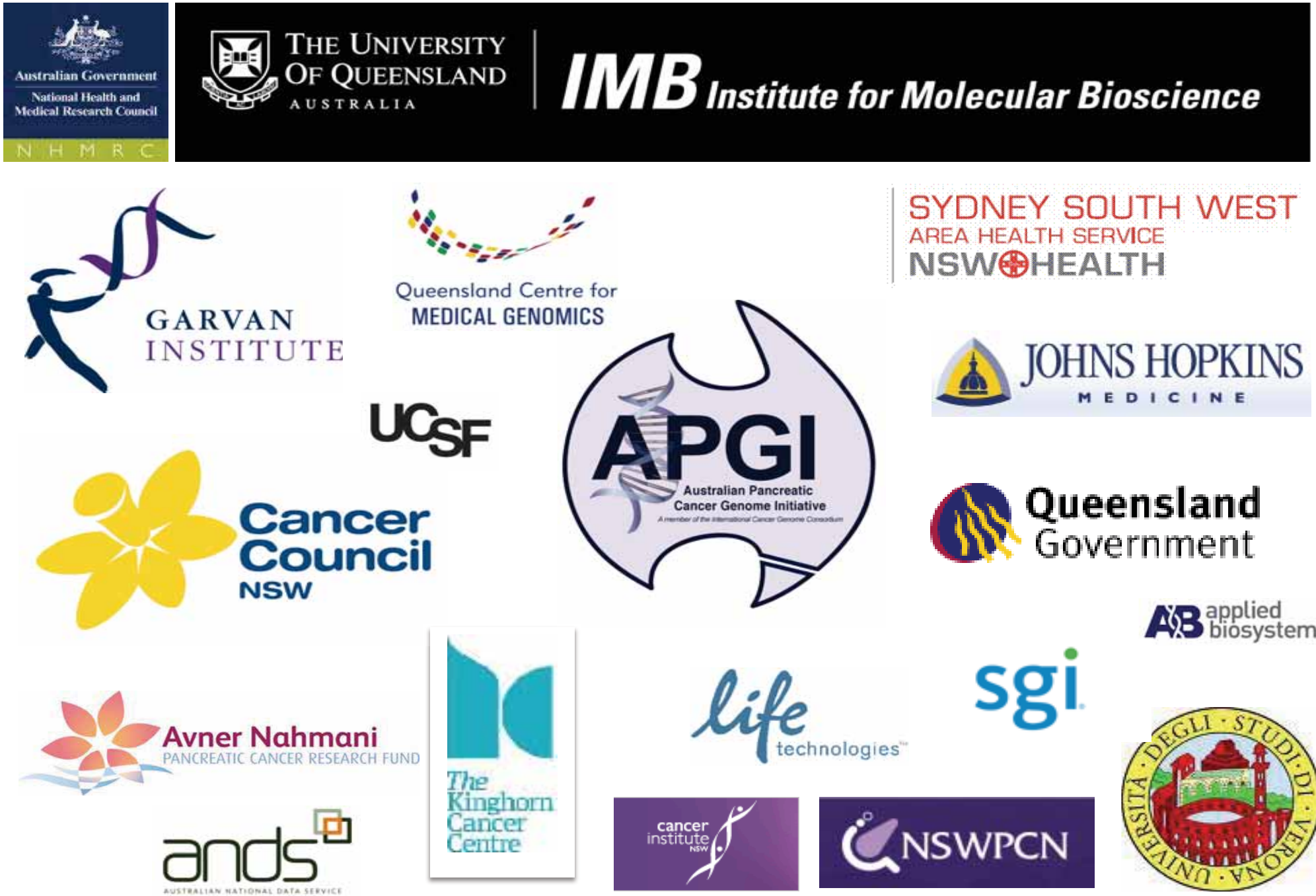
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Thank you for your attention

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