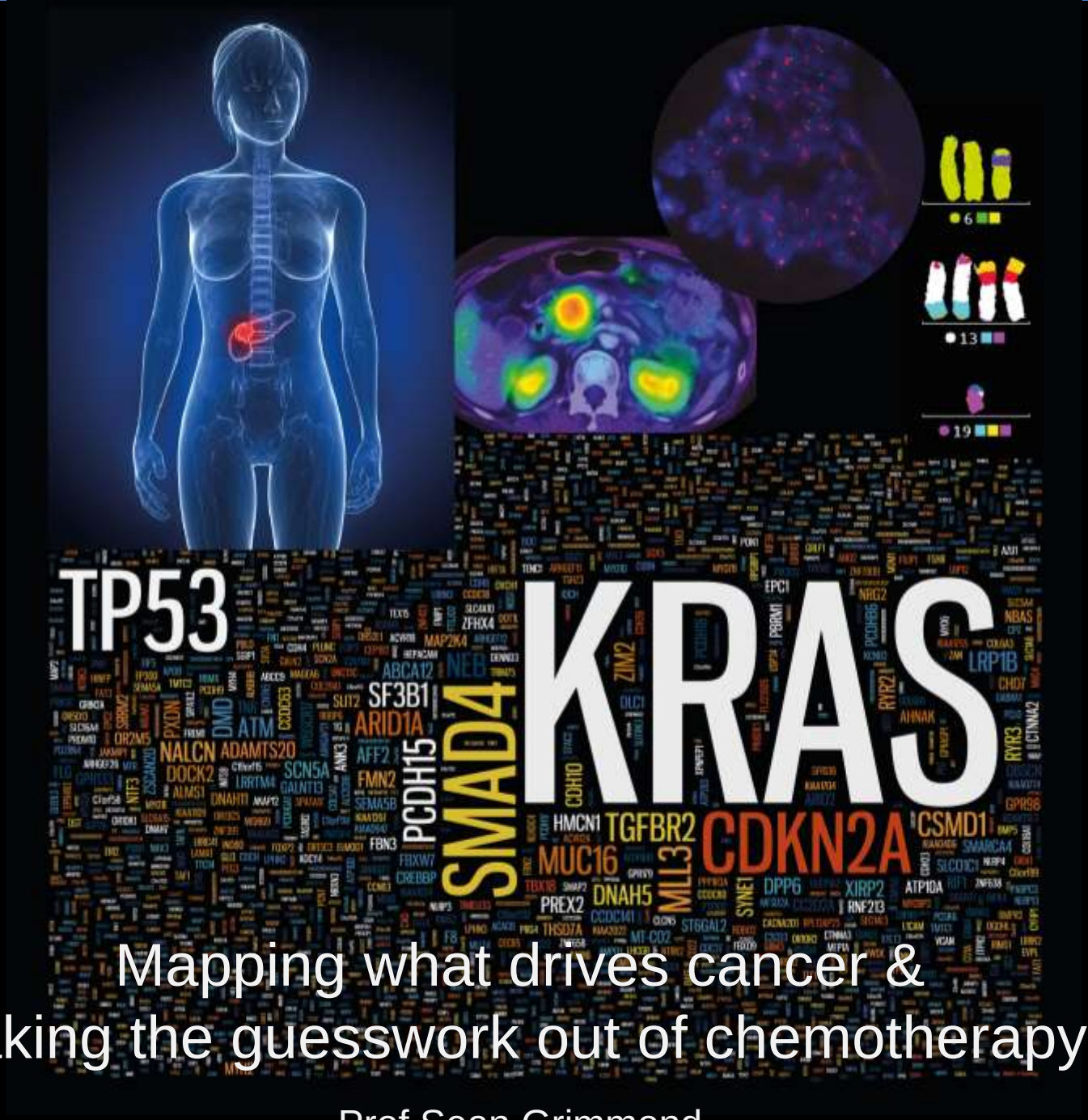


Mapping what drives cancer & taking the guesswork out of chemotherapy

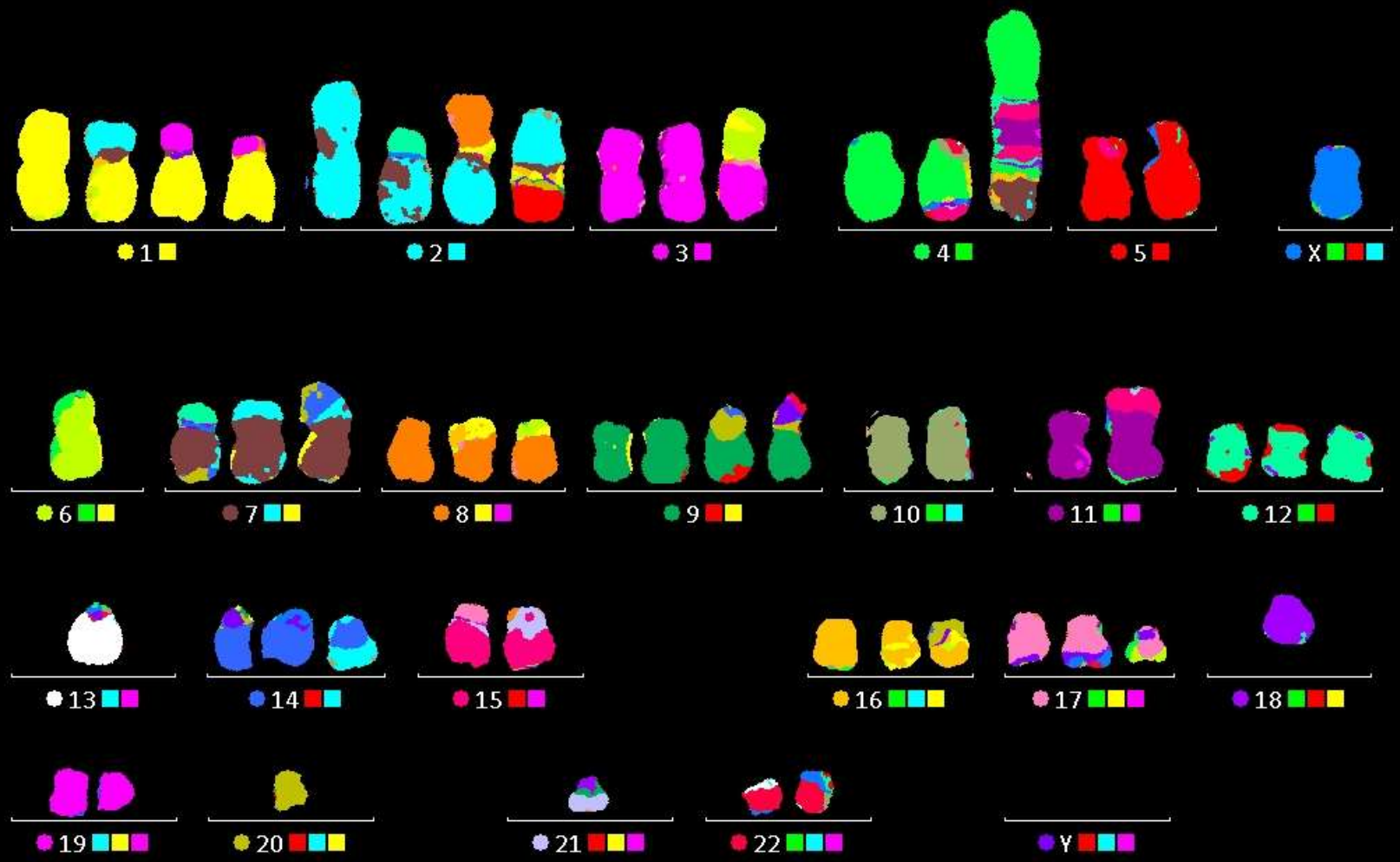
Prof Sean Grimmond

- **Understanding the molecular basis of cancer**

- **Using Genomics to map out what drives each cancer type**

- **The International Cancer Genome Consortium**

- **Using cancer atlases to find the Achilles' Heel in cancers, one patient at a time**


1
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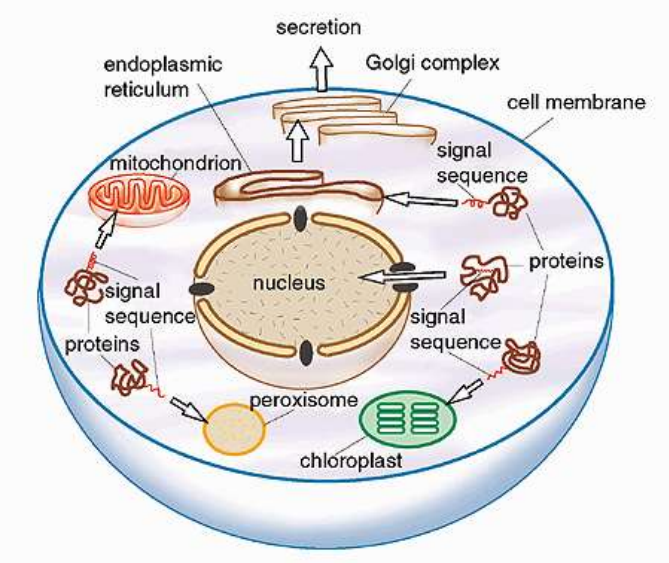
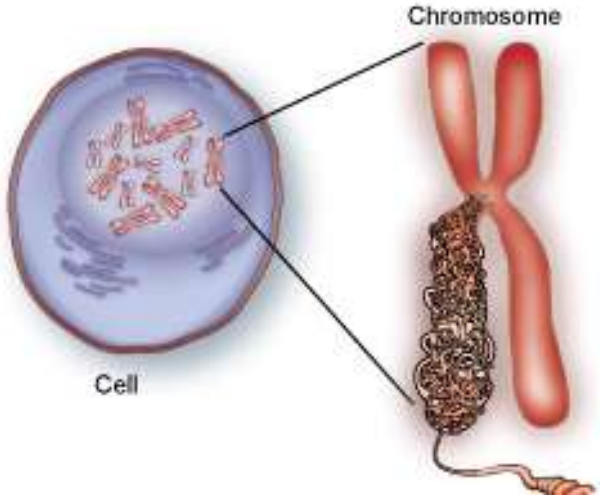
22
Y

APGI-2057:


?14
mar1
mar2
mar3
mar4
mar5

DNA: The cell's computer hard drive





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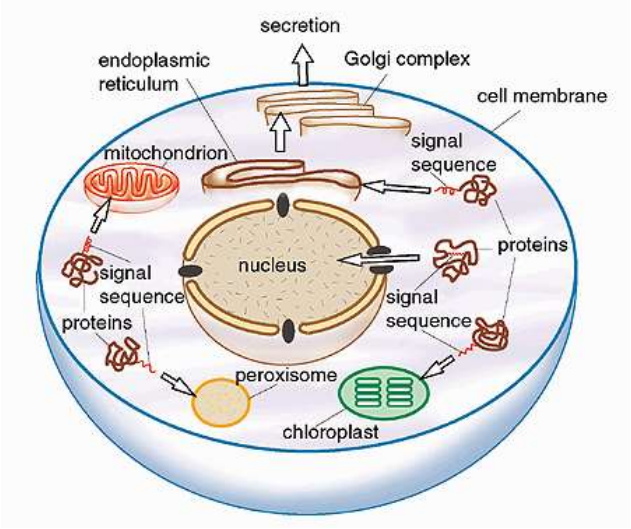
DNA: The cell's computer hard drive



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3,000,000,000,000 bases,
23 chromosomes,
30,000 genes
1,000s of gene networks

3,000,000,000 bits of data
23 partitions to the drive,
30,000 files
1,000s of programs

Tempting fate with your computer ….

Change code

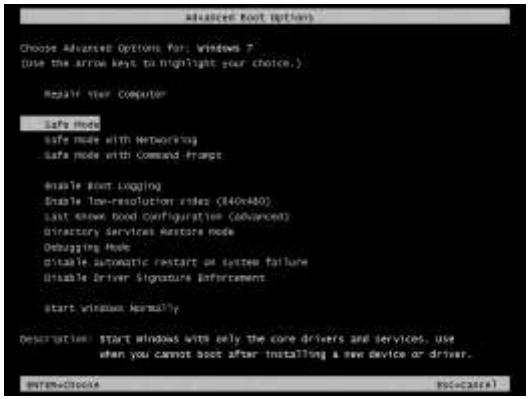
Rearrange code

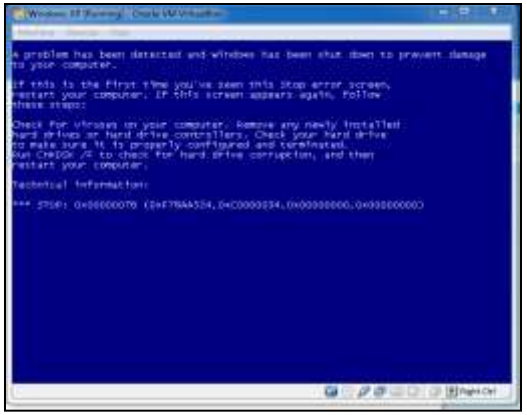
Delete files

Move files

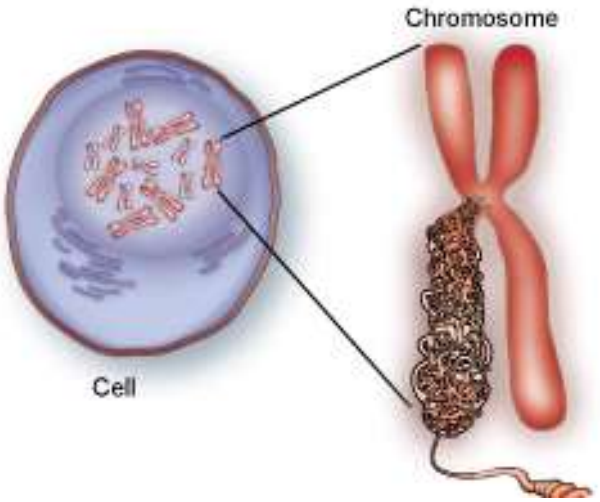
Make extra copies

Join files…





Tempting fate with your cell's hard drive….



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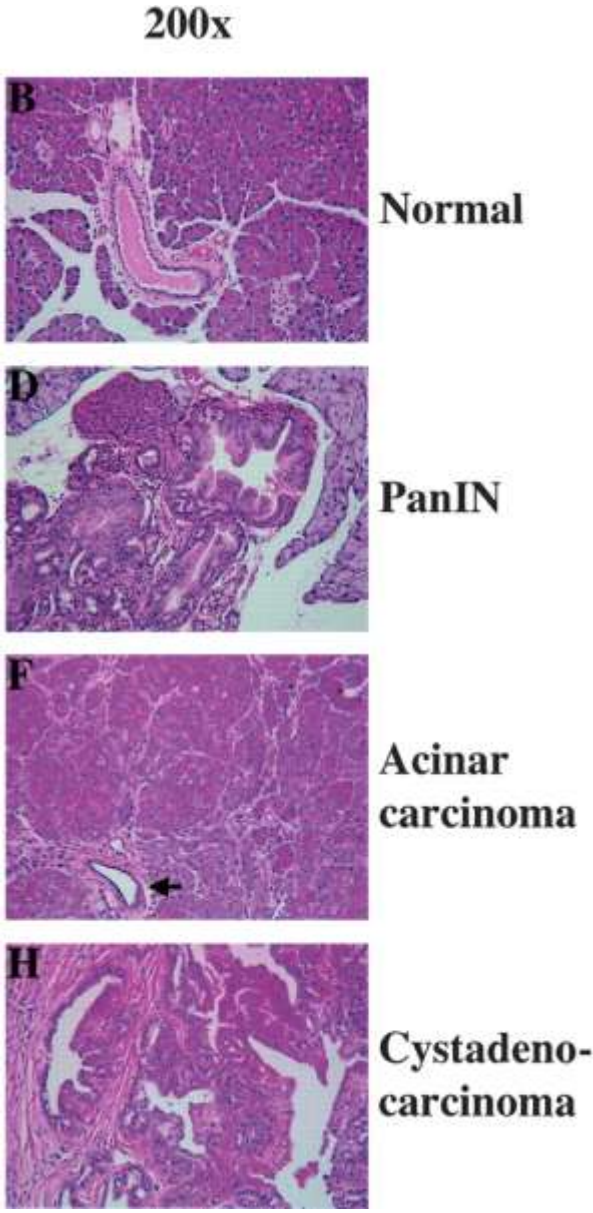
Change code
Rearrange code
Delete genes
Move genes
Make extra copies
Join genes…



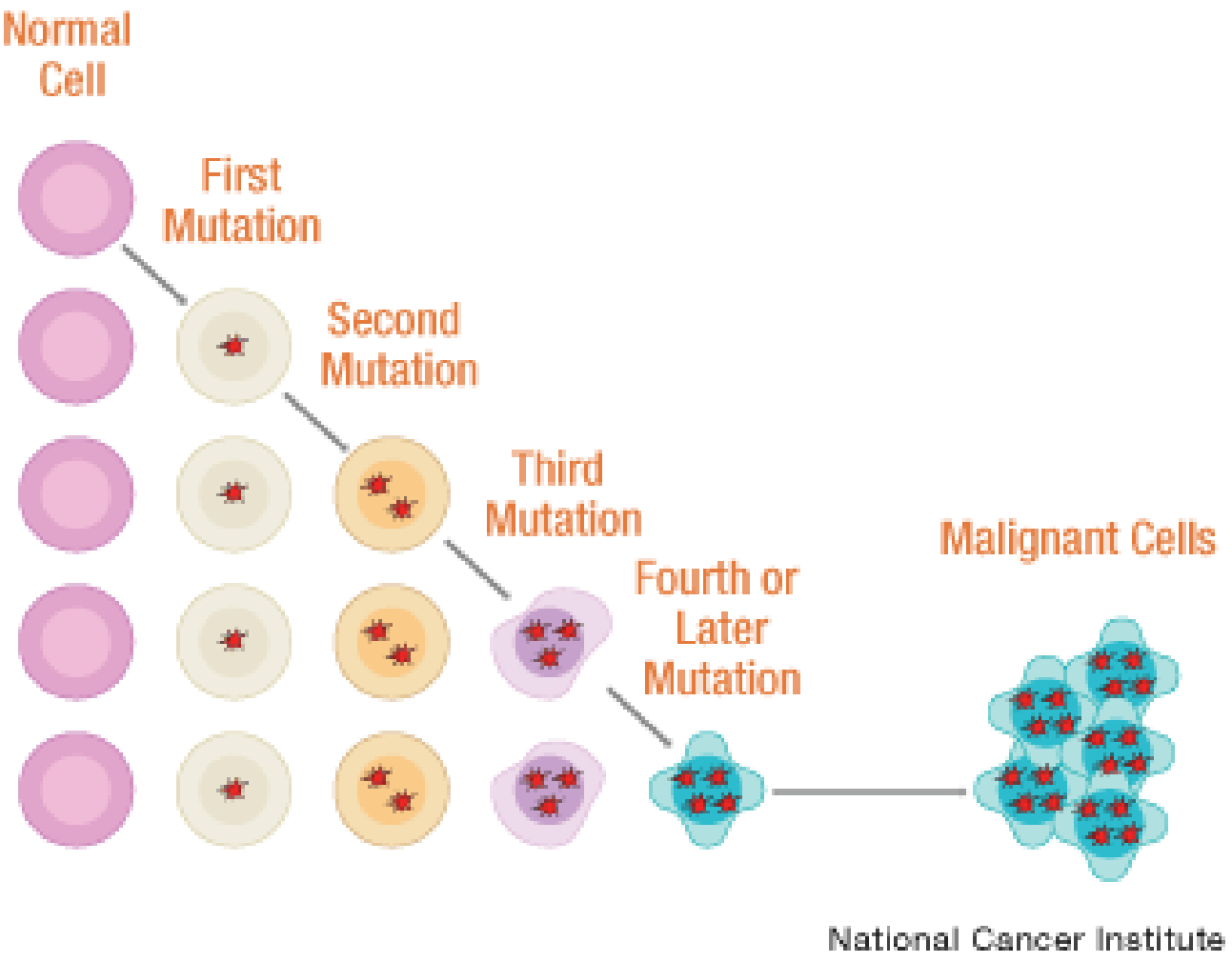
Cancer arises due to accumulated damage to D

Relax DNA repair

Over-ride built in senescence

Acquire a continuous Growth Signal

Turn off “internal Suicide” system



Mutagens, radiation, inflammation
Random DNA damage

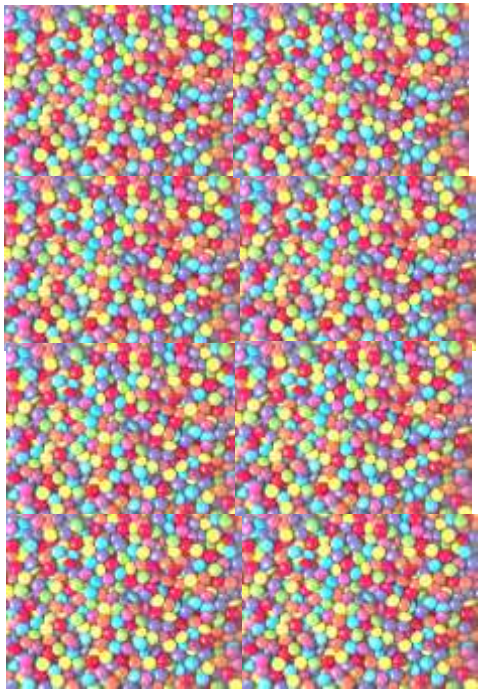
Decoding a Cancer Genomes

1. Create 2 heaps of 320,000 copies of a 24 jigsaw puzzles (2,000,000 *double sided* jigsaw puzzles- all of the same sort of picture)….

2. Randomly sample 1,000,000,000 pieces from each pile.

3. Match the pieces back using the the pictures on the boxes despite 50,000,000 pieces looking identical to 1000s locations on the main picture and 20,000,000 pieces having random printing errors.

4. Find the 30 pieces with deliberate changes in some of the "tumour" puzzle only….



Genomics Revolution

Human Genome Project:

International effort
US$2billion
(1991-2003)

Wolfson Wohl Cancer Centre: £5000
Monday-Sunday.

2015: WWCRC @£1500
Monday-Wednesday

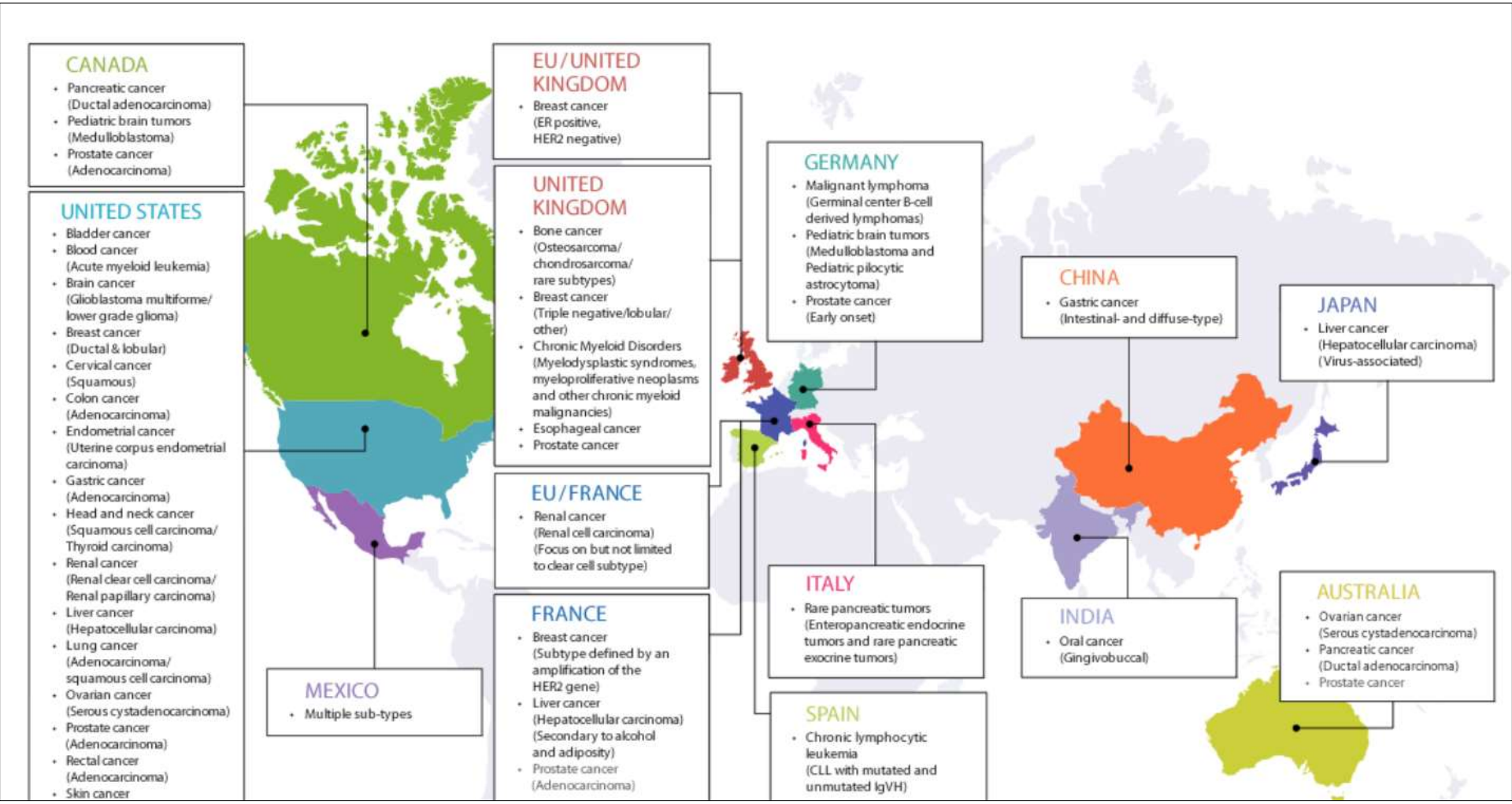
International Cancer Genome Consortium

ICGC Goal:

- **To obtain a comprehensive description of all genomic changes in 50 different tumor types and/or subtypes which are of clinical and societal importance across the globe.**

- **500 tumours per tumour type/subtype**

http://icgc.org



Currently committed: 37 projects, >17,000 patients.

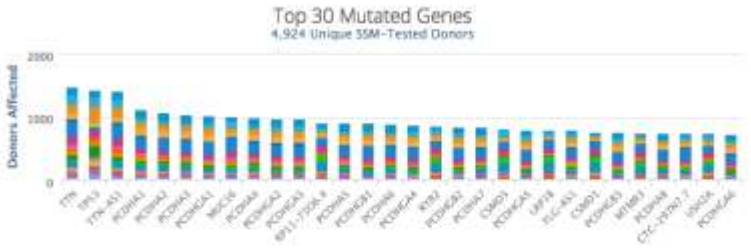
Queensland Centre for MEDICAL GENOMICS

ICGC Data Portal

Quick Search

CANCER PROJECTS

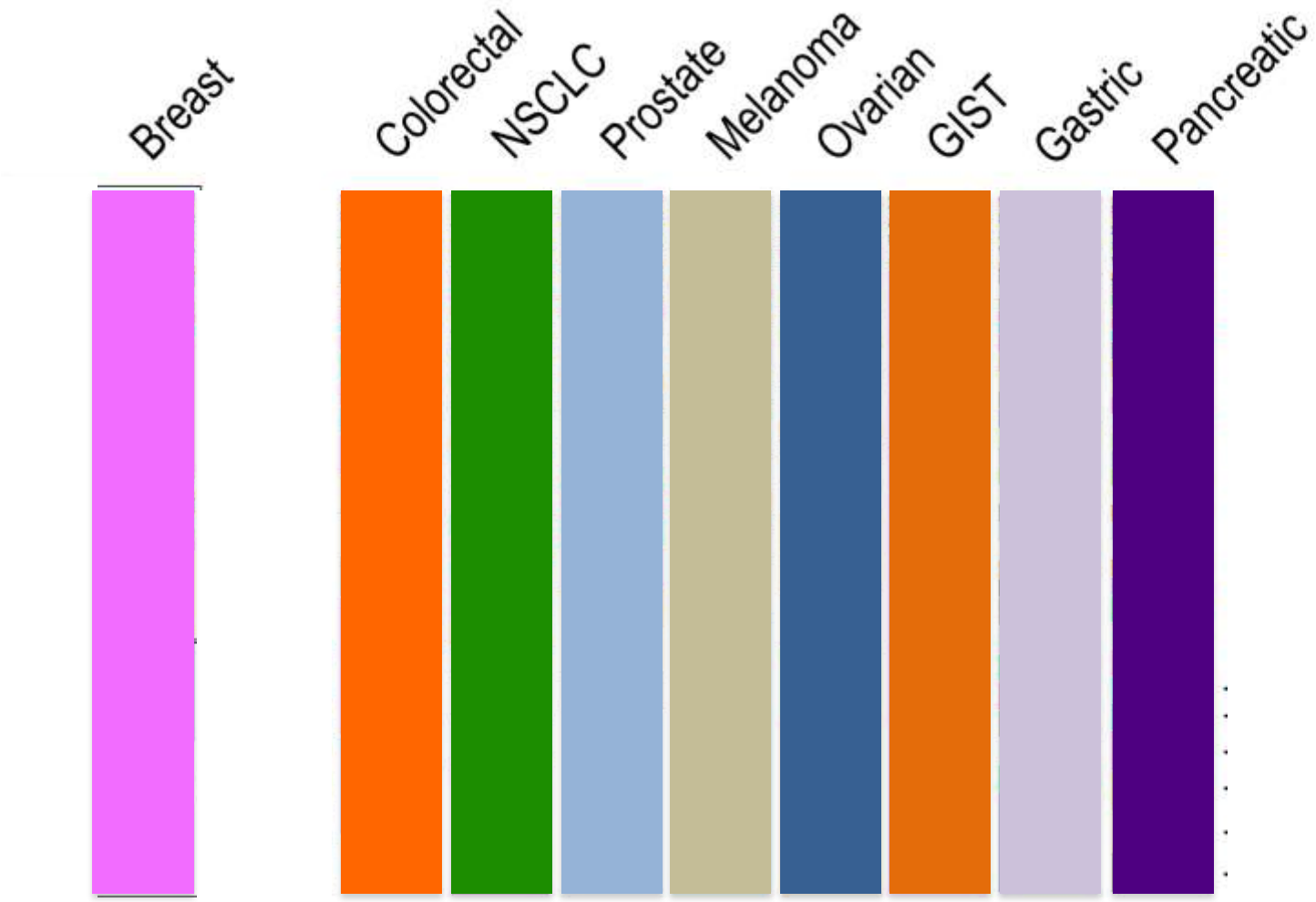
- Primary Site
  - Pancreas 4
  - Liver 4
  - Kidney 4
  - Head and n... 4
  - Brain 4
  - *13 more*
- Cancer Project
  - BLCA-US 1
  - BOCA-UK 1
  - BRCA-UK 1
  - BRCA-US 1
  - CESC-US 1
  - *37 more*
- Countries
  - United States 22
  - United King... 4
  - Germany 3
  - Australia 3
  - Japan 2
  - *7 more*
- Available Data Types
  - SSM 32
  - CNSM 32
  - EXP 26
  - METH 23
  - miRNA 20
  - *3 more*



Showing **42** projects

Code	Name	Site	Country	Donors	Available Data Types						
					SSM	CNSM	StSM	SGV	METH	EXP	PEXP
BRCA-US	Breast Cancer - TC...	Breast	United States	977	766	976	--	--	862	958	29
KIRC-US	Kidney Renal Clear...	Kidney	United States	505	404	500	--	--	490	498	45
THCA-US	Head and Neck Th...	Head and neck	United States	487	392	486	--	--	424	479	21
SKCM-US	Skin Cutaneous m...	Skin	United States	320	308	317	--	--	211	314	19
GBM-US	Brain Glioblastoma...	Brain	United States	577	267	567	--	--	385	555	21
PACA-AU	Pancreatic Cancer -...	Pancreas	Australia	351	252	133	106	--	--	177	--
UCEC-US	Uterine Corpus En...	Uterus	United States	480	246	479	--	--	462	472	20
LINC-JP	Liver Cancer - NCC, JP	Liver	Japan	244	244	--	--	--	--	--	--
COAD-US	Colon Adenocarcin...	Colorectal	United States	435	216	416	--	--	402	402	29
PBCA-DE	Pediatric Brain Can...	Brain	Germany	306	196	4	4	--	115	--	--
LUSC-US	Lung Squamous C...	Lung	United States	408	178	408	--	--	326	403	19
PRAD-US	Prostate Adenocar...	Prostate	United States	175	166	174	--	--	155	174	13
LIRI-JP	Liver Cancer - RIKE...	Liver	Japan	158	158	--	--	--	--	--	--
CMDI-UK	Chronic Myeloid Di...	Blood	United Kingdom	129	129	--	--	--	--	--	--
BRCA-UK	Breast Triple Negat...	Breast	United Kingdom	141	117	112	45	--	--	--	--
CLLE-ES	Chronic Lymphocy...	Blood	Spain	264	109	4	--	--	139	225	--
RECA-EU	Renal Cell Cancer - ...	Kidney	France European Union	122	95	--	--	--	--	91	--
OV-AU	Ovarian Cancer - AU	Ovary	Australia	93	91	93	74	--	--	--	--

Cancer is Complex



ICGC
TCGA

A New Vision for Clinical and Translational Cancer Research

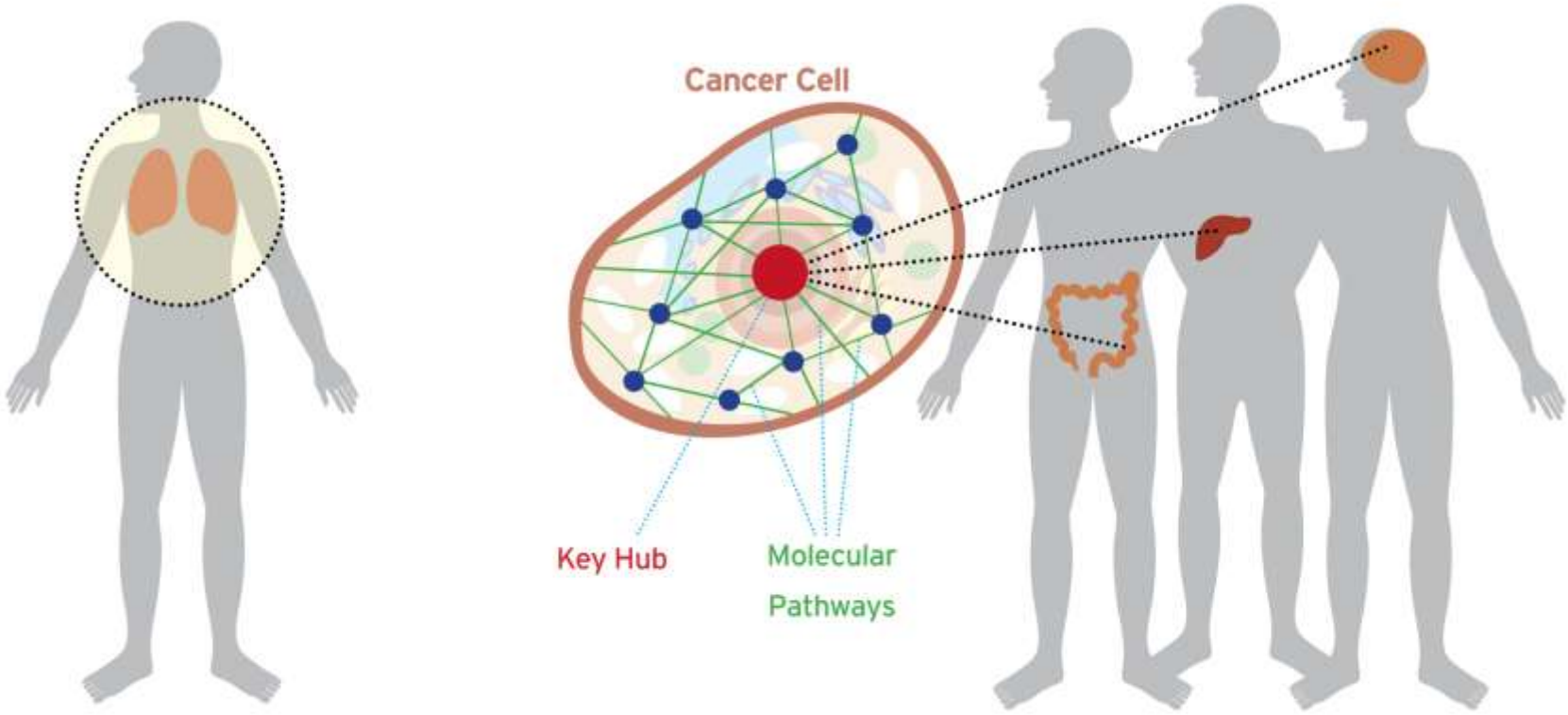
"We can no longer think of cancer as one disease. Even something like lung cancer could be hundreds of distinct cancers, each defined by specific molecular characteristics requiring different treatment approaches. This makes research more challenging, but the payoff for patients will be enormous."

MICHAEL P. LINK, MD, PRESIDENT OF ASCO

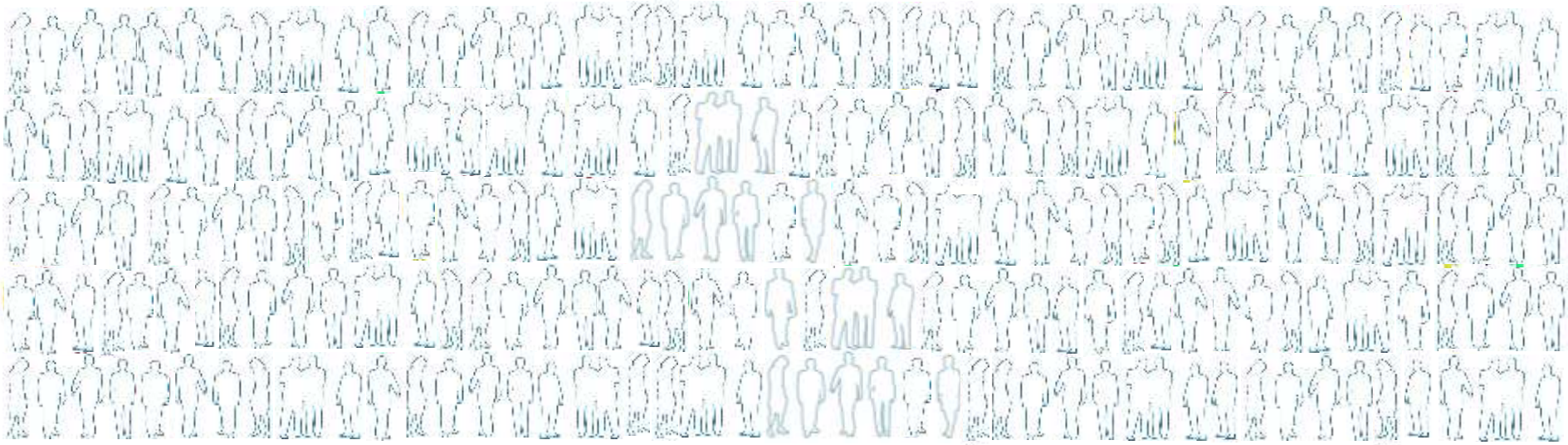
A New Model for Therapeutic Development

OLD MODEL: Treatment is determined by a tumor's location in the body, without regard to the molecular charateristics of the patient or the tumor.

NEW MODEL: Treatment is determined by key molecular "hubs" that must be targeted within the cells, and is only administered to patients whose tumors are found to have those hubs – potentially without regard to the tumor's location in the body.



Genome Directed Oncology



Mutation-Drug1

Mutation-Drug2

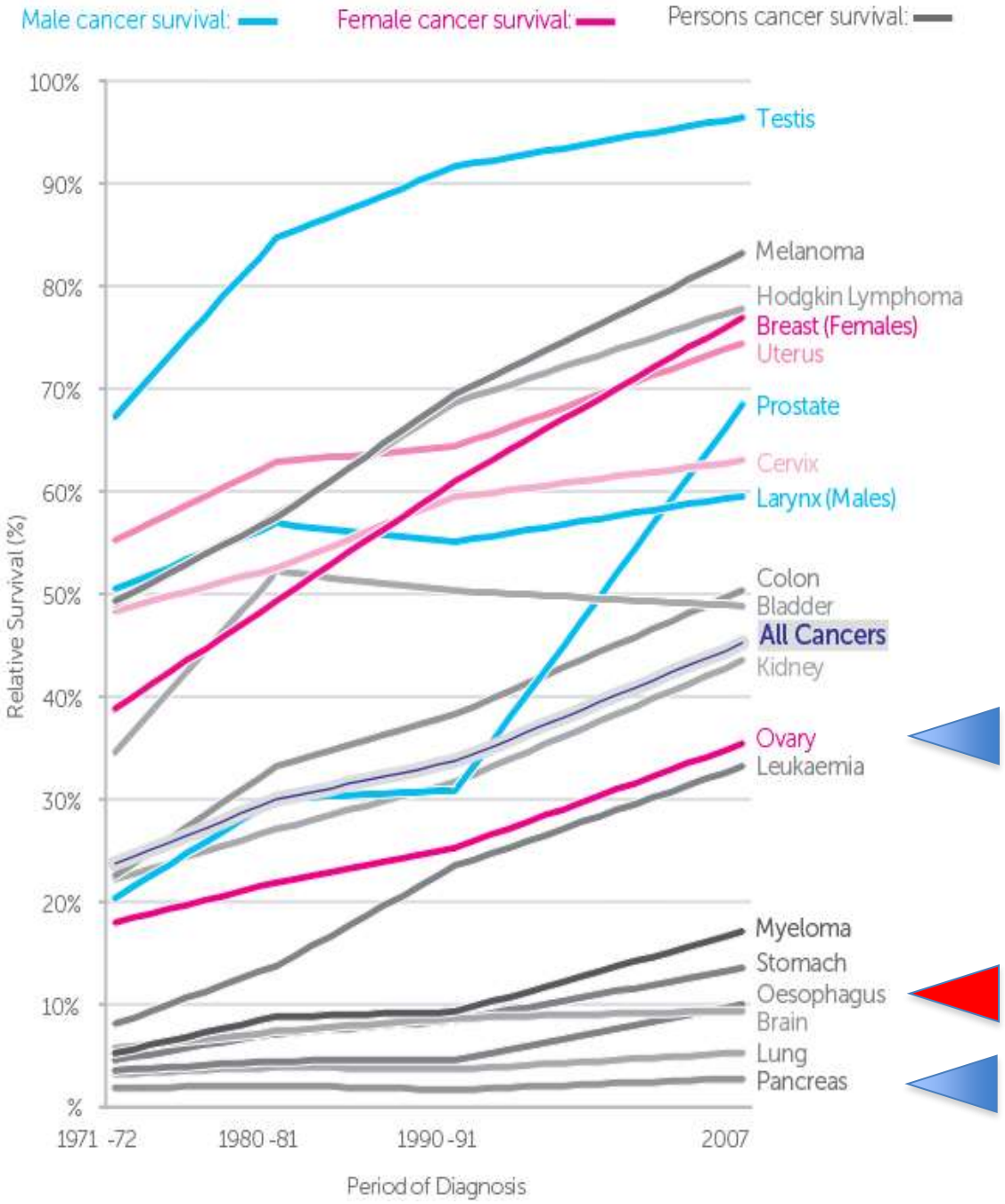
Mutation-Drug3

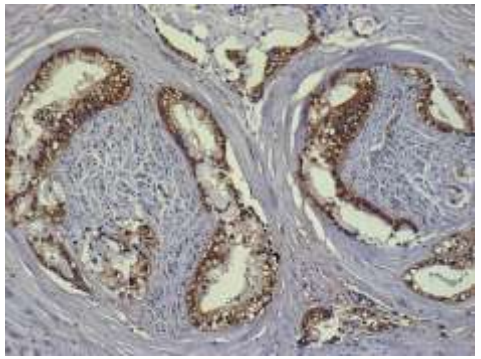
Mutation-Drug4

Novel Targets and Drugs

Andrew Biankin

Molecular Phenotyping for all candidate targets


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

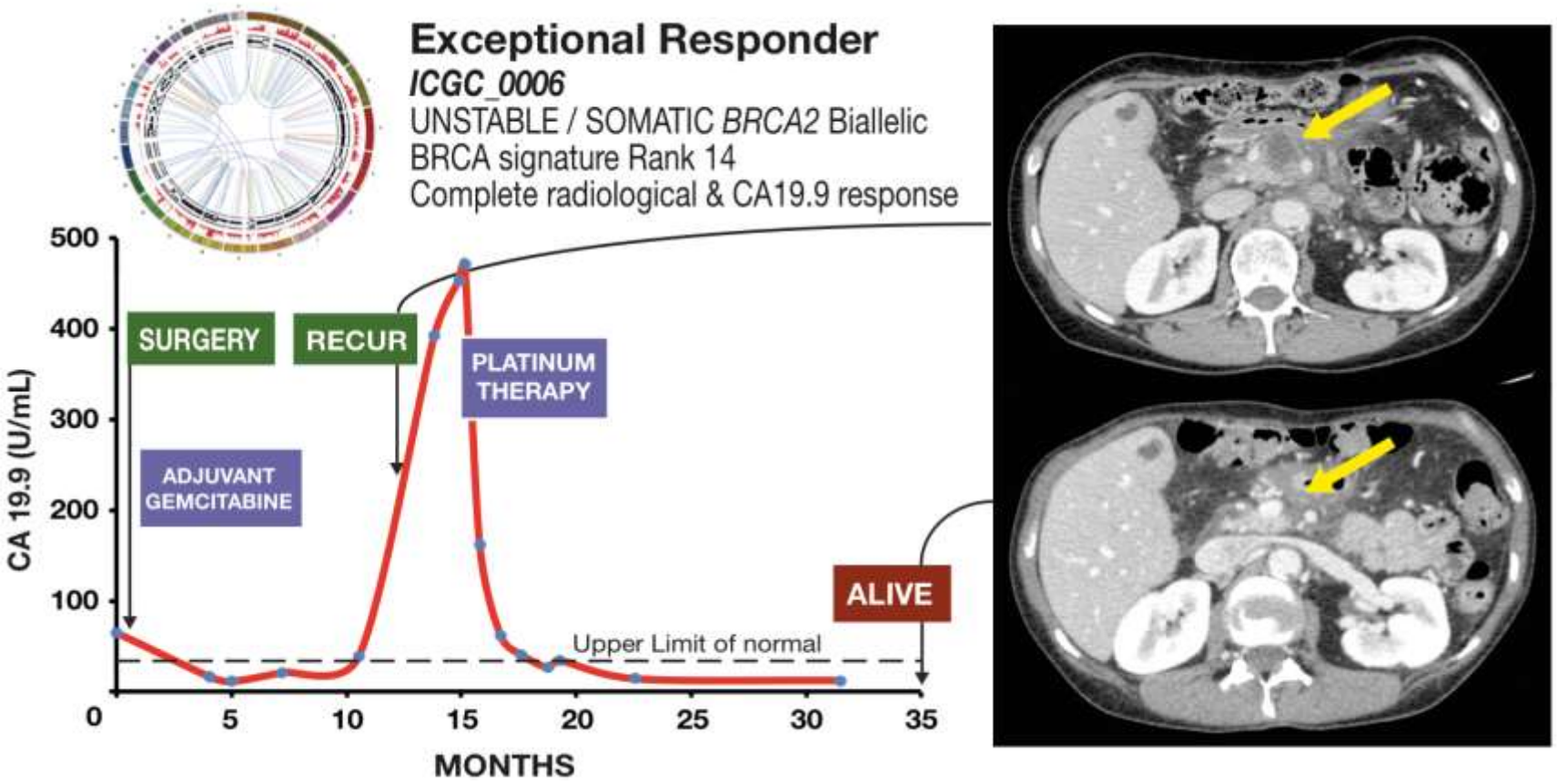


Are there therapeutic targets for PDAC?

1. DNA damage repair defect: 10%**
2. RNF43 mutation: 8%*
3. RNA processing defects: 8%*
4. ROBO-SLIT-SRGAP mutation: 7%*
5. ATM mutation: 6%**
6. SMARCA4 defects: 5%
7. RICTOR mutations: 3%**
8. HER2 Amplification: 3%**
9. MET Amplification: 2%**
10. KRAS wildtype**: 5%**
11.

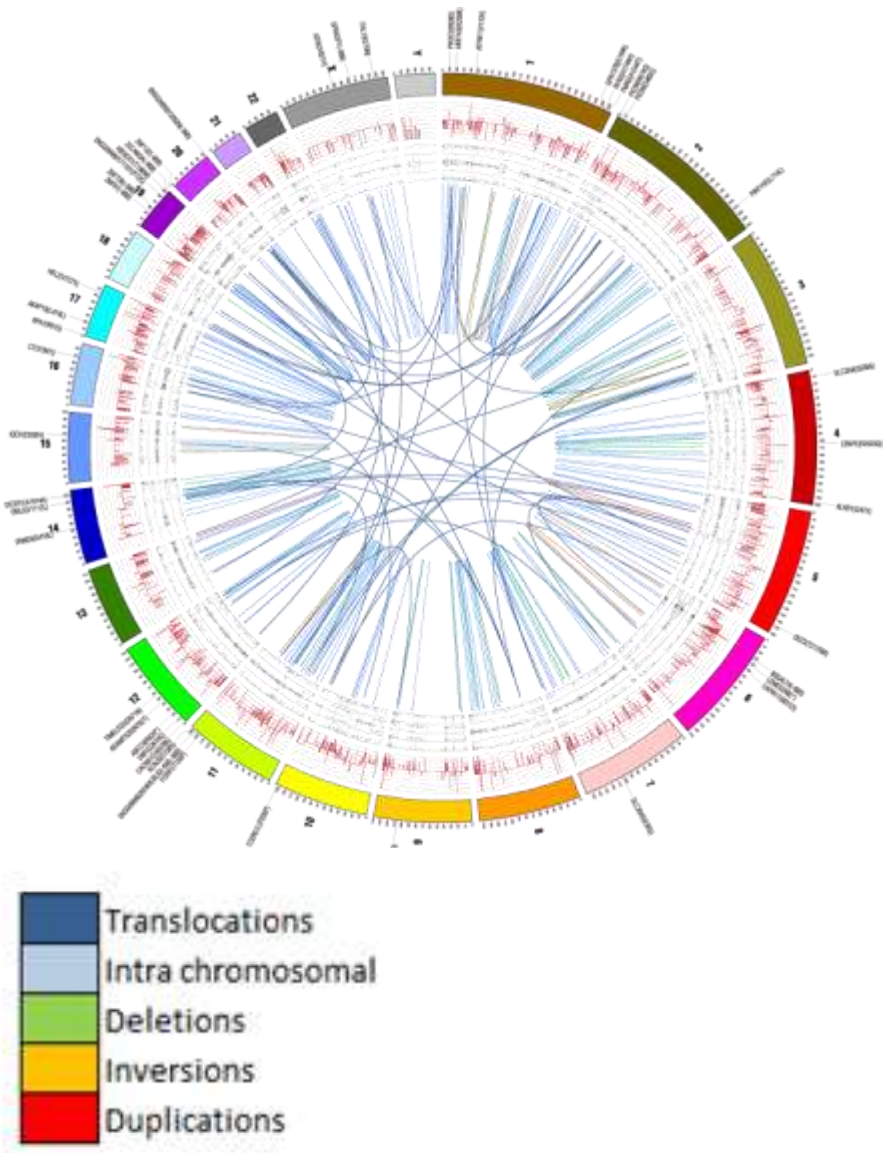
Chang et al, 2014

Exceptional PDAC responder:



David Chang

Patient Cancer Genome Report: APGI-1992



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

CANCER RESEARCH UK

CRUK GLASGOW CENTRE

Andrew Biankin
Sean Grimmond
Jeff Evans
Owen Sansom
Eyal Gottlieb
David Chang
Oliver Hofmann
James Paul
Judith Dixon
Jennifer Morton

CRUK MANCHESTER INSTITUTE

Claus Jorgensen
Caroline Dive
Juan Valle

CRUK CAMBRIDGE CENTRE

Duncan Jodrell
Doug Fearon
Pippa Corrie
Ashok Venkitaraman
Bristi Basu
Simon Cook

CRUK OXFORD CENTRE

Eric O'Neil
Somnath Mukherjee
Ruth Muschel

CRUK BARTS CENTRE

Thorsten Hagemann
John Marshall
Nick Lemoine
Christopher Heeschen
Kairbaan Hodivala Dilke
Hemant Kocher

NCRI AstraZeneca MedImmune

- **Recent advances in Genome science are making it possible to determine the molecular basis of a patient's cancer.**

- **International efforts to build large cancer genome atlases that stands to become the foundations for cancer research for the next decade.**

- **These technological advances are starting to provide tangible clinical benefit (cancer surveillance, and improving treatment selection).**