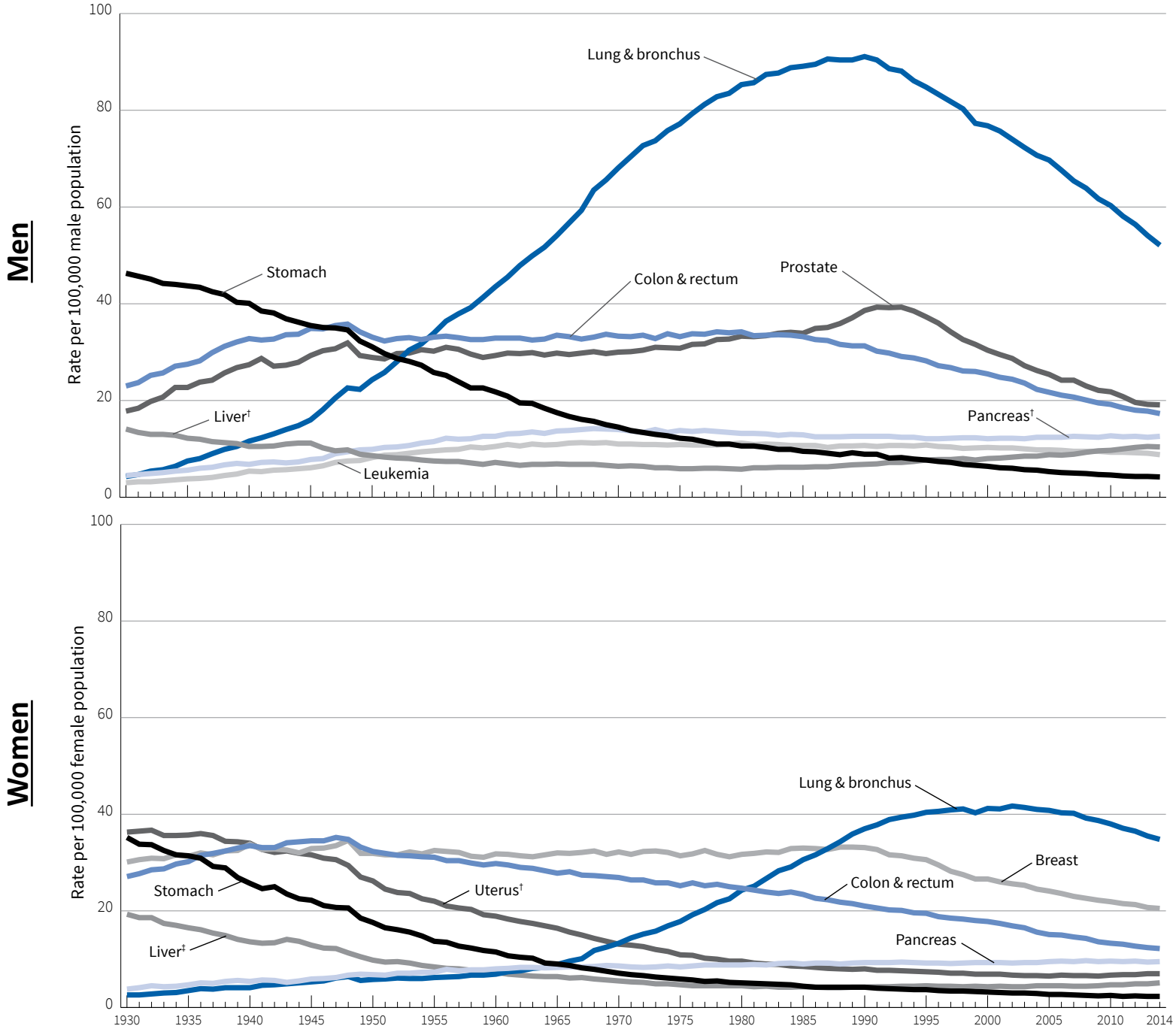
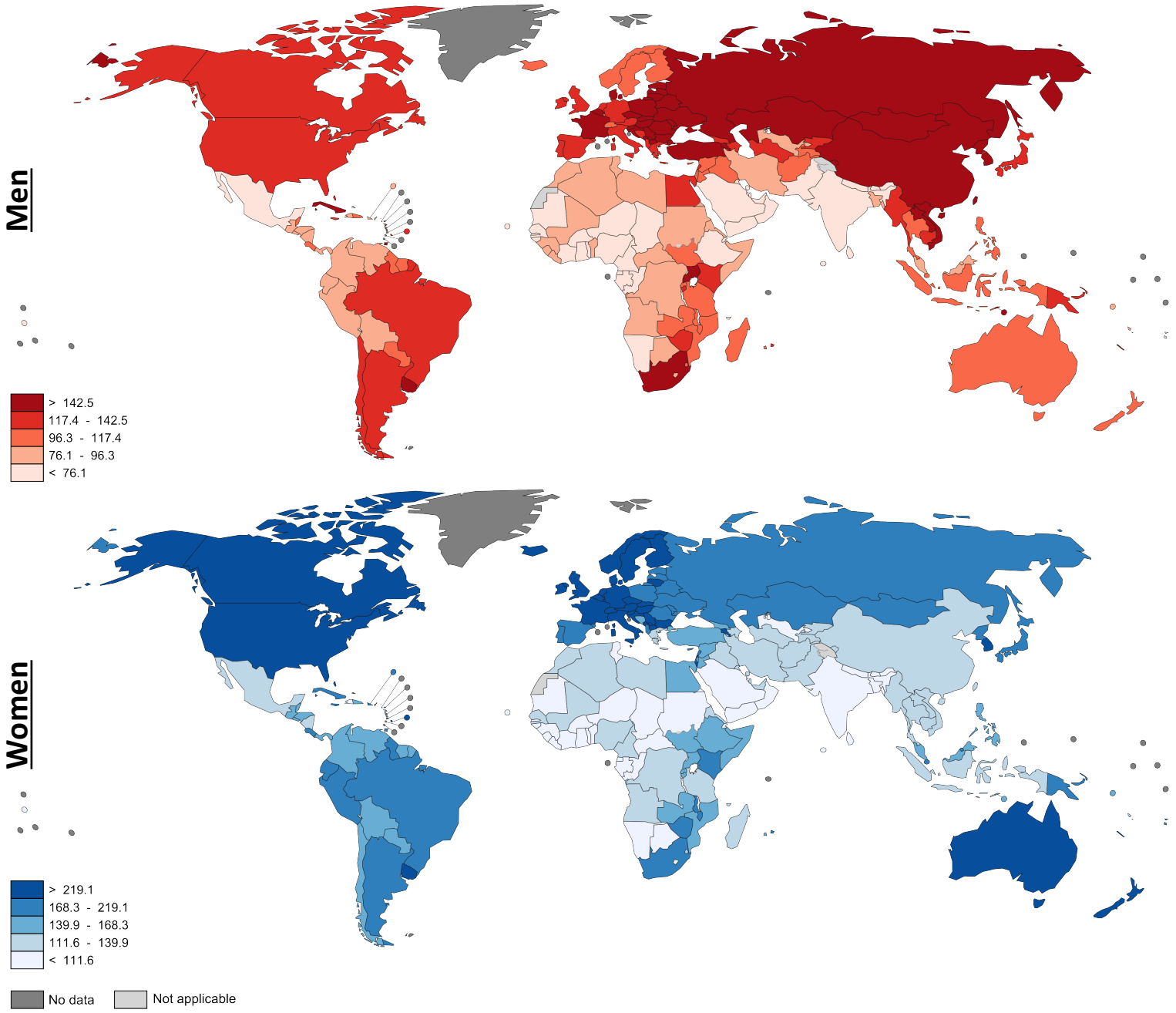
Epidemiology of cancer-related mortality rates in the United States (1930-2014)



Source: ACS, US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2014, National Center for Health Statistics, Centers for Disease Control and Prevention.

Estimated Cancer Incidence Worldwide (2012)



Source: World Health Organization

Goals of the The Cancer Moonshot Initiative

Accelerate progress in cancer, including prevention & screening

- From cutting-edge basic research to wider uptake of standard care

Encourage greater cooperation and collaboration

- Break down silos within and between academia, government, and private sector

Enhance data sharing

- Accessible data that is universally usable
- Annotated patient-level clinical and –omics data

- Adapted from Presidential Memo and Factsheet, 2016

Summary of the 10 Recommendations

A. Establish a network for **direct patient involvement**
B. Create a translational science network devoted to **immunotherapy**
C. Develop ways to overcome **resistance to therapy**
D. Build a national cancer **data ecosystem**
E. Intensify research of the major drivers of **childhood cancer**
F. Minimize cancer treatment's debilitating **side effects**
G. Expand use of proven **prevention and early detection** strategies
H. Mine past patient data to predict future **patient outcomes**
I. Develop a 3D **cancer atlas**
J. Develop new cancer **technologies**

Summary of the 10 Recommendations

A. Establish a network for direct patient involvement

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I. Develop a 3D cancer atlas

J. Develop new cancer technologies

Intensify research of the major drivers of childhood cancer

- Goal – Accelerate the development of new therapies that target these cancer-causing proteins

- **Fusion oncoproteins**
  - Enhance understanding of molecular and biochemical mechanisms of transformation driven by fusion oncoproteins
  - Develop faithful models
  - Identify key dependencies

Develop a 3D cancer atlas

- Goal – Enable predictive models of tumor progression and response to treatment

- **Generation of human tumor atlases**
  - Adult and pediatric cancers
  - From tumor development through metastasis
  - Immune cell characterization and other cells in the microenvironment
  - Premalignant lesions to create a Pre-Cancer Genome Atlas (PCGA)

Precision Medicine Initiative

"To enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized care."

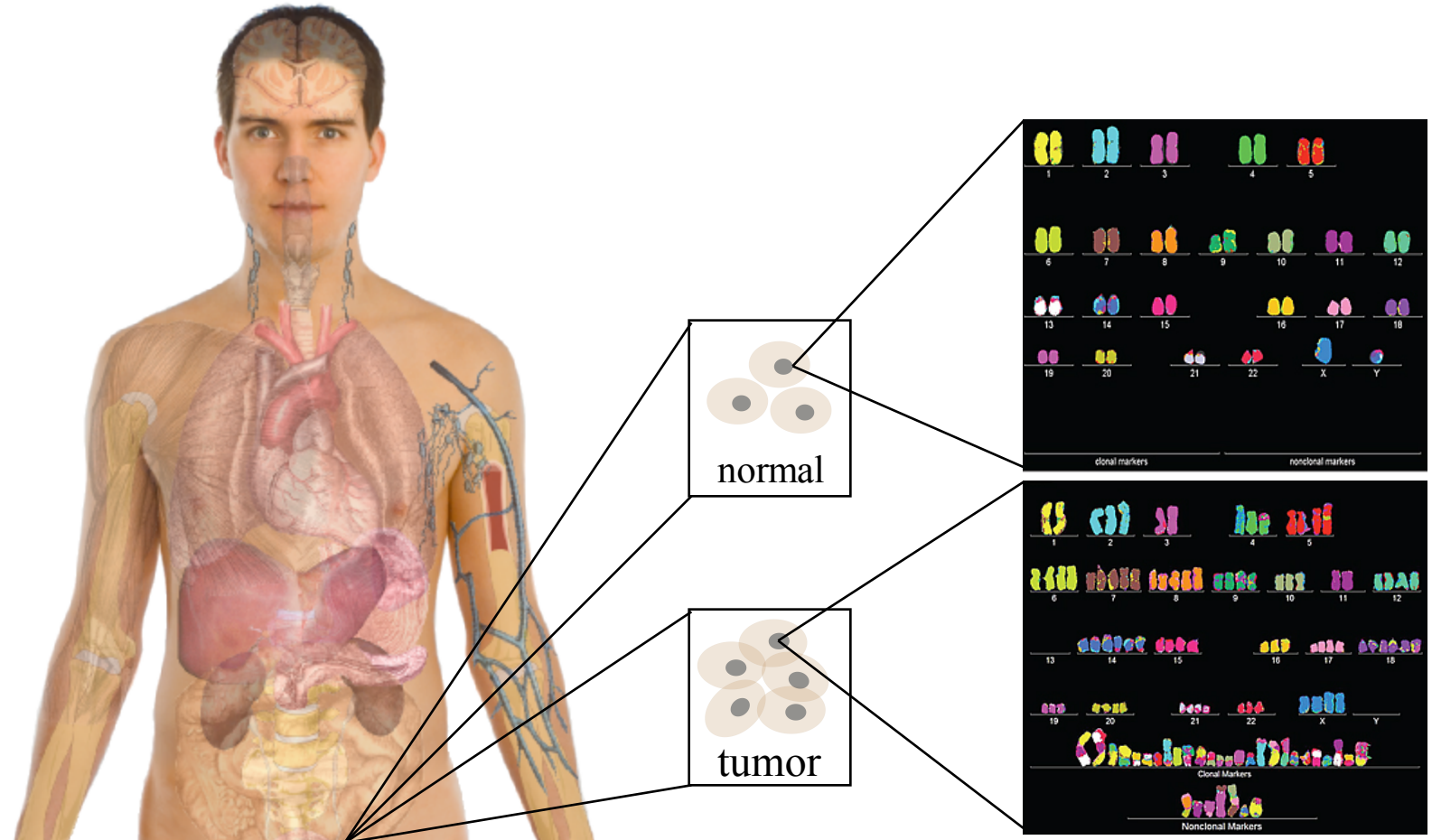
- Barak Obama

THE PRECISION MEDICINE INITIATIVE

$215 million was invested (NIH fiscal year 2016) to accelerate research for selecting the therapies that can be used in more individualized ways. NCI used $70 million of that investment to advance the precision oncology.

Personal Genomics as a Gateway into Biology

Personal genomes soon will become a commonplace part of medical research & eventually treatment (esp. for cancer). They will provide a primary connection for biological science to the general public.



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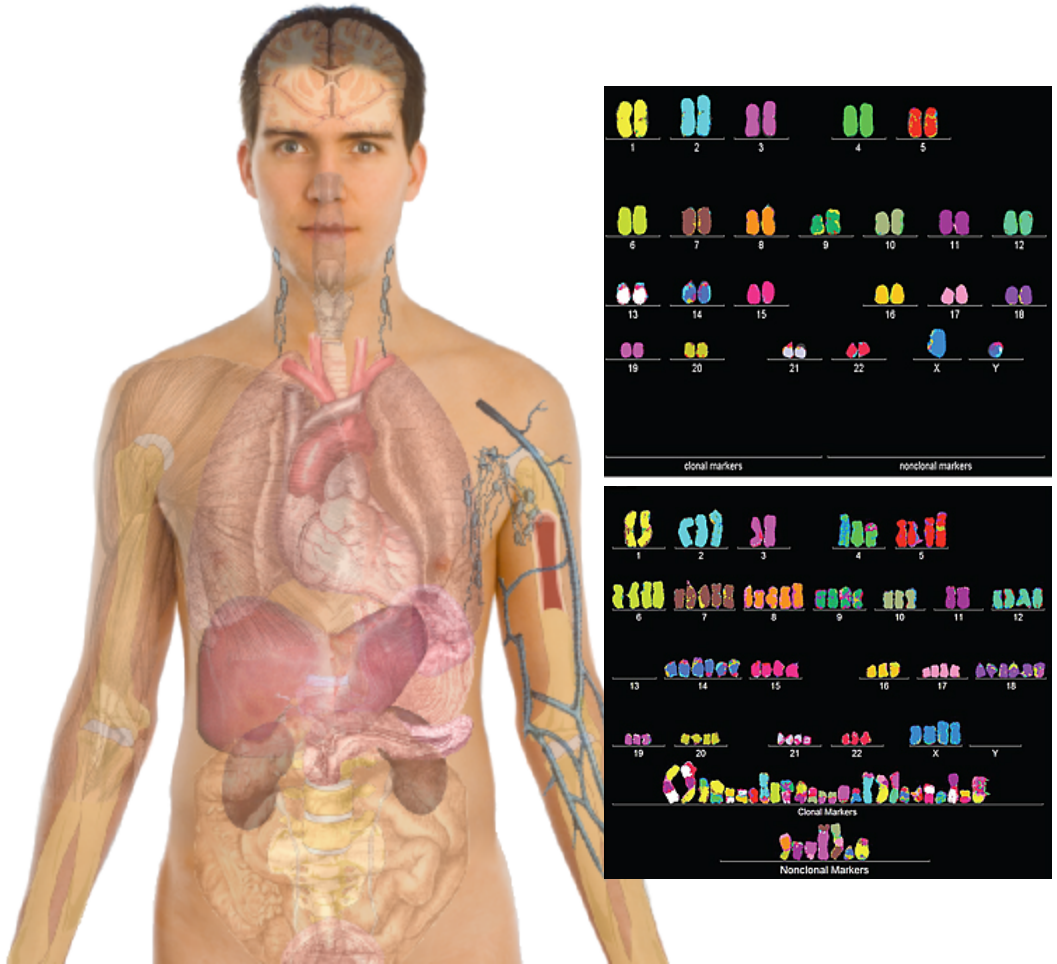
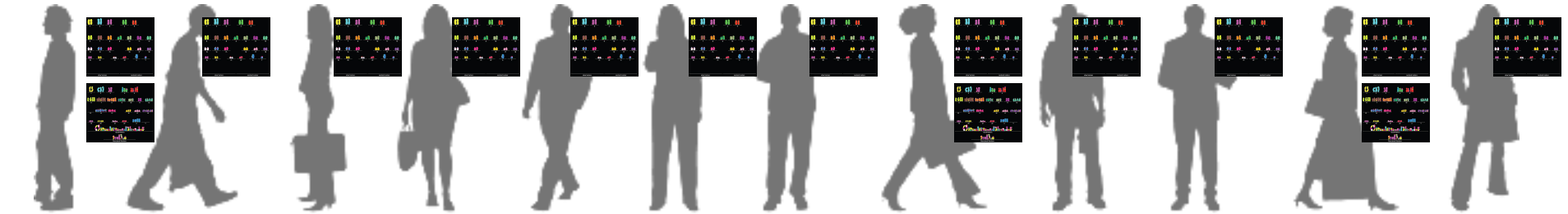
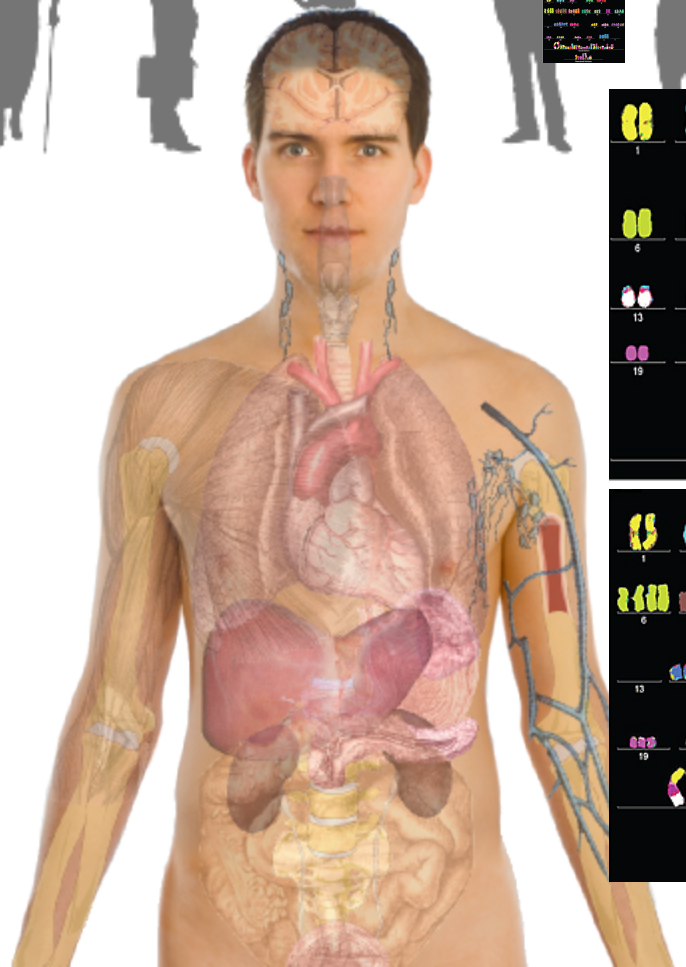
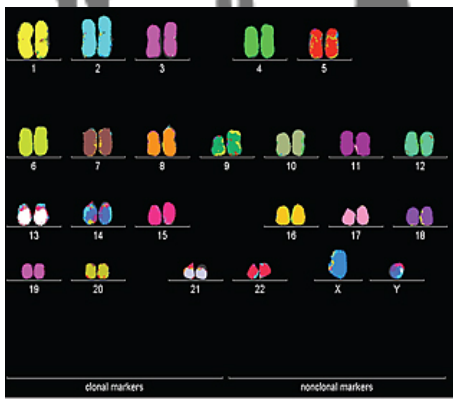


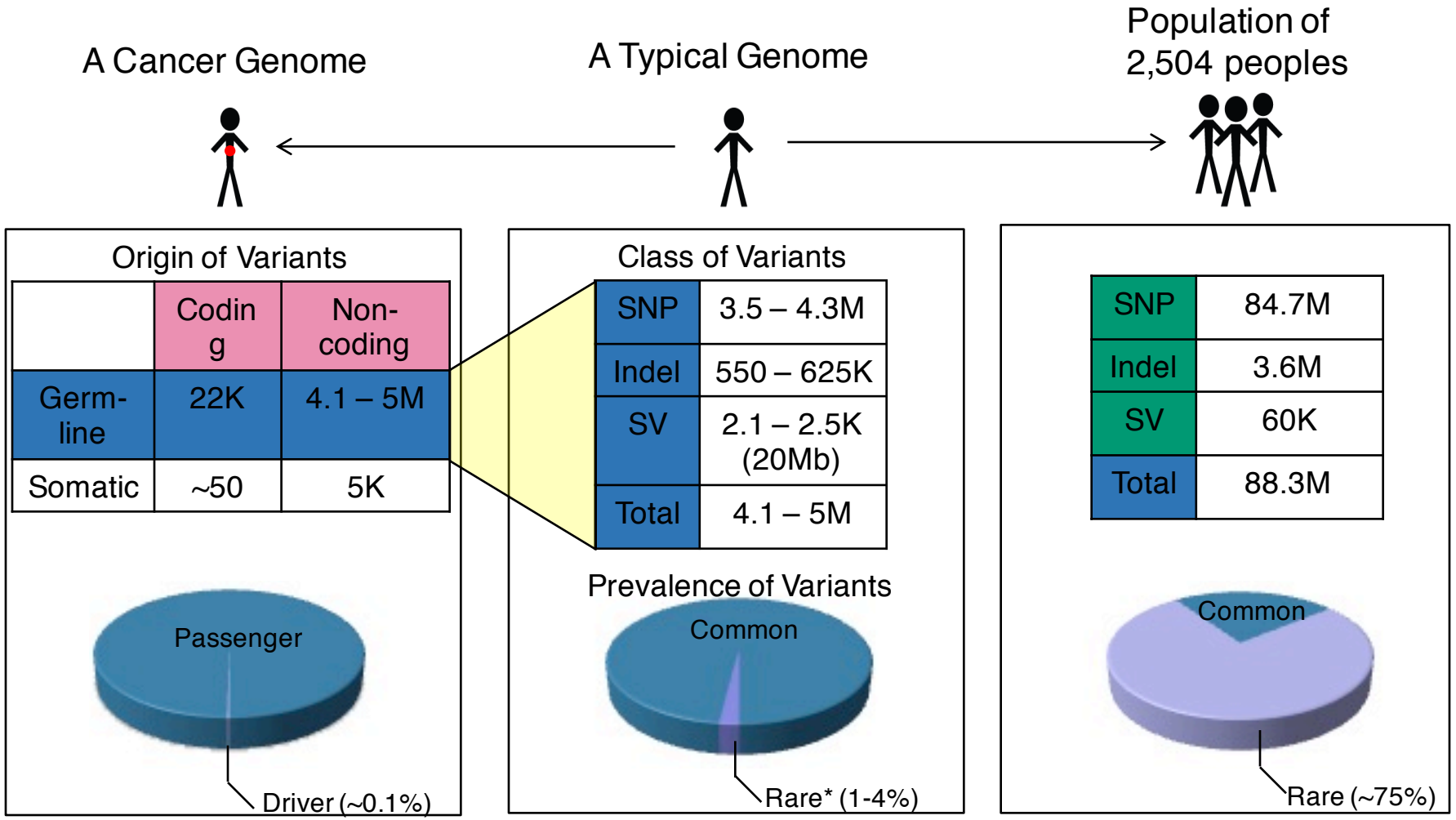





clonal markers
nonclonal markers


Clonal Markers
Nonclonal Markers

Human Genetic Variation

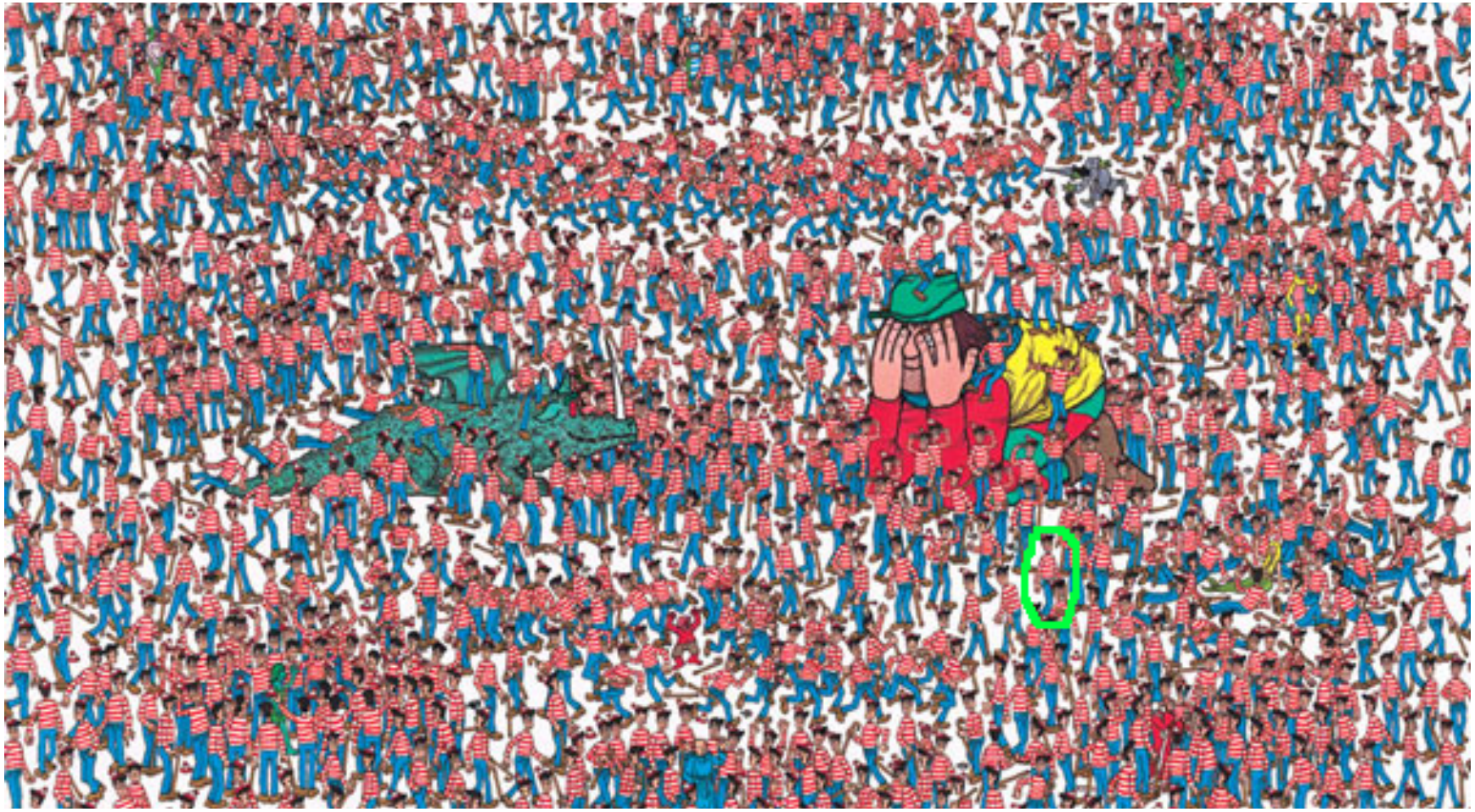


* Variants with allele frequency < 0.5% are considered as rare variants in 1000 genomes project.

The 1000 Genomes Project Consortium, Nature. 2015. 526:68-74
Khurana E. et al. Nat. Rev. Genet. 2016. 17:93-108

Cancer drivers: Significance & identification

(Finding the key mutations in ~3M Germline variants &
~5K Somatic Variants in a Tumor Sample)



Finding Key Variants

Germline

CAN YOU FIND THE PANDA?

- **Common variants**
  - Can be associated with phenotype (ie disease) via a Genome-wide Association Study (GWAS), which tests whether the frequency of alleles differs between cases & controls.
  - Usually their functional effect is weaker.
  - Many are non-coding
  - Issue of LD in identifying the actual causal variant.
- **Rare variants**
  - Associations are usually underpowered due to low frequencies.
  - They often have larger functional impact
  - Can be collapsed in the same element to gain statistical power (burden tests).
  - In some cases, causal variants can be identified through tracing inheritance of Mendelian subtypes of diseases in large families.

McCarthy, M. et al. Nat. Rev. Genet. 2008. 9, 356-369, Zuk, O. et al. PNSA. 2014. Vol. 11, no. 4, MacArthur DG et al. Nature 2014. 508:469-476

Cancer drivers: Significance & identification

Finding Key Variants

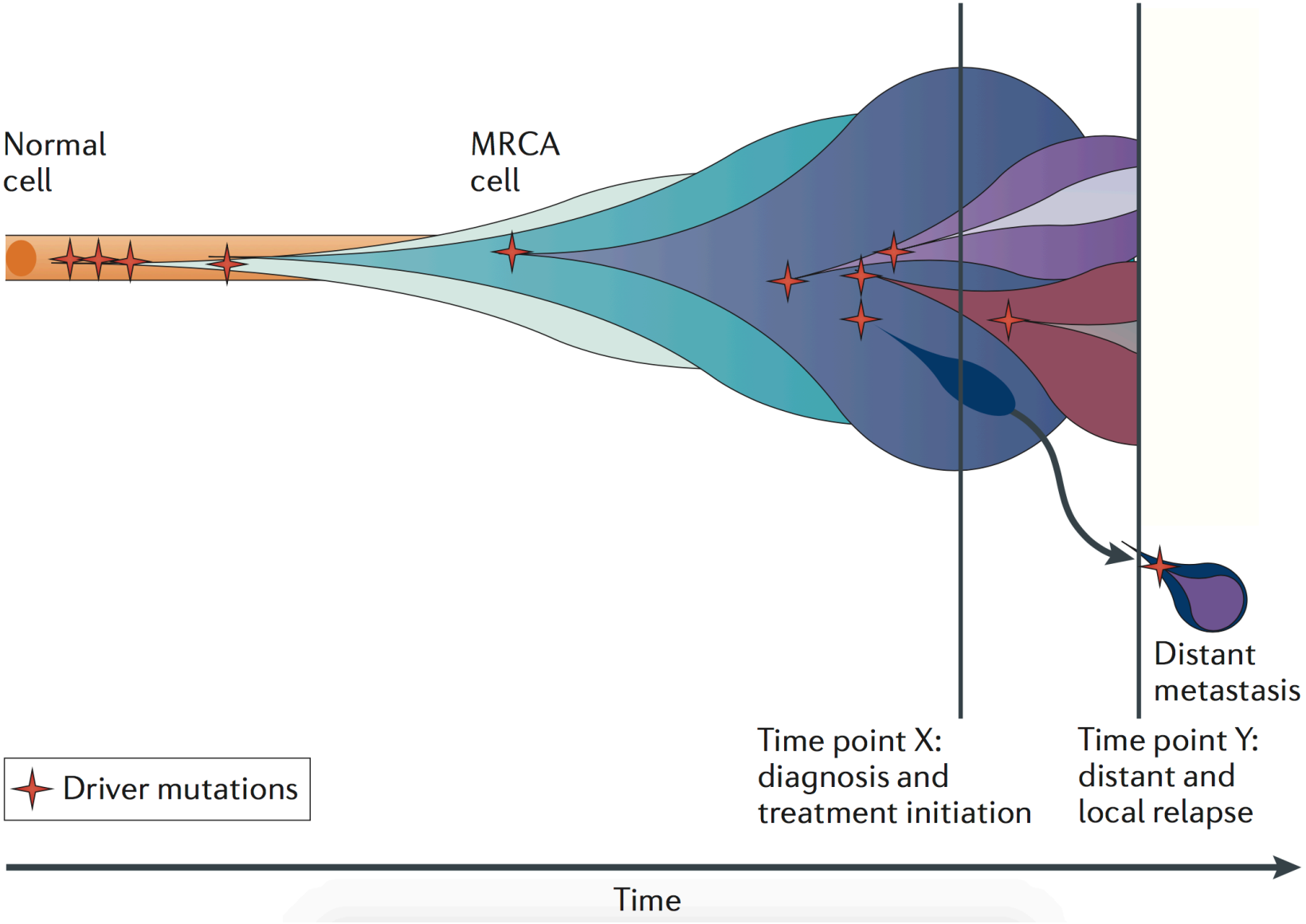
Somatic

CAN YOU FIND THE PANDA?

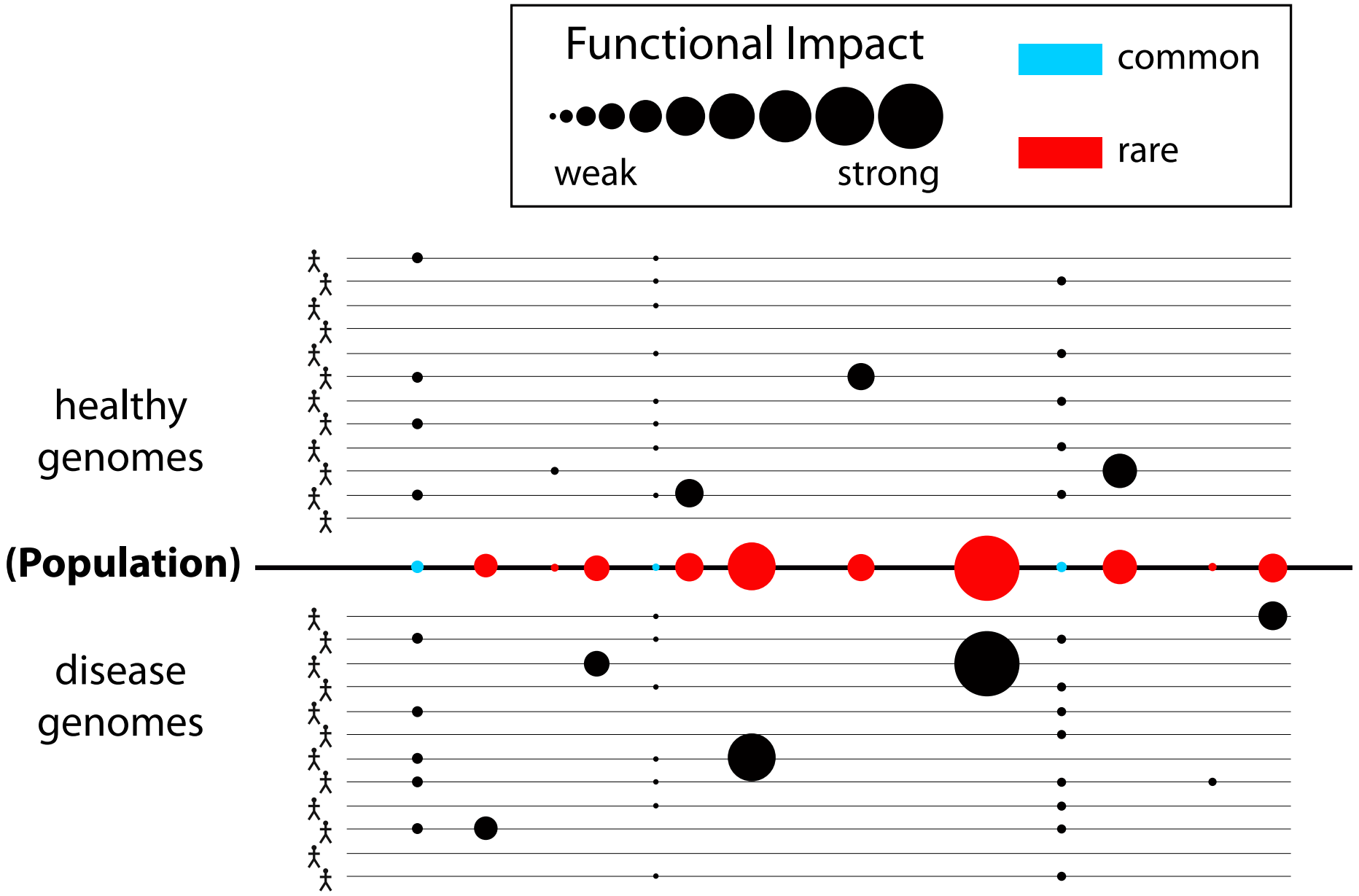
- **Overall**
  - Often these can be conceptualized as very rare variants
  - A challenge to identify somatic mutations contributing to cancer is to find driver mutations & distinguish them from passengers.
- **Drivers**
  - Driver mutation is a mutation that directly or indirectly confers a selective growth advantage to the cell in which it occurs.
  - A typical tumor contains 2-8 drivers; the remaining mutations are passengers.
- **Passengers**
  - Conceptually, a passenger mutation has no direct or indirect effect on the selective growth advantage of the cell in which it occurred.

Vogelstein B. Science 2013. 339(6127):1546-1558

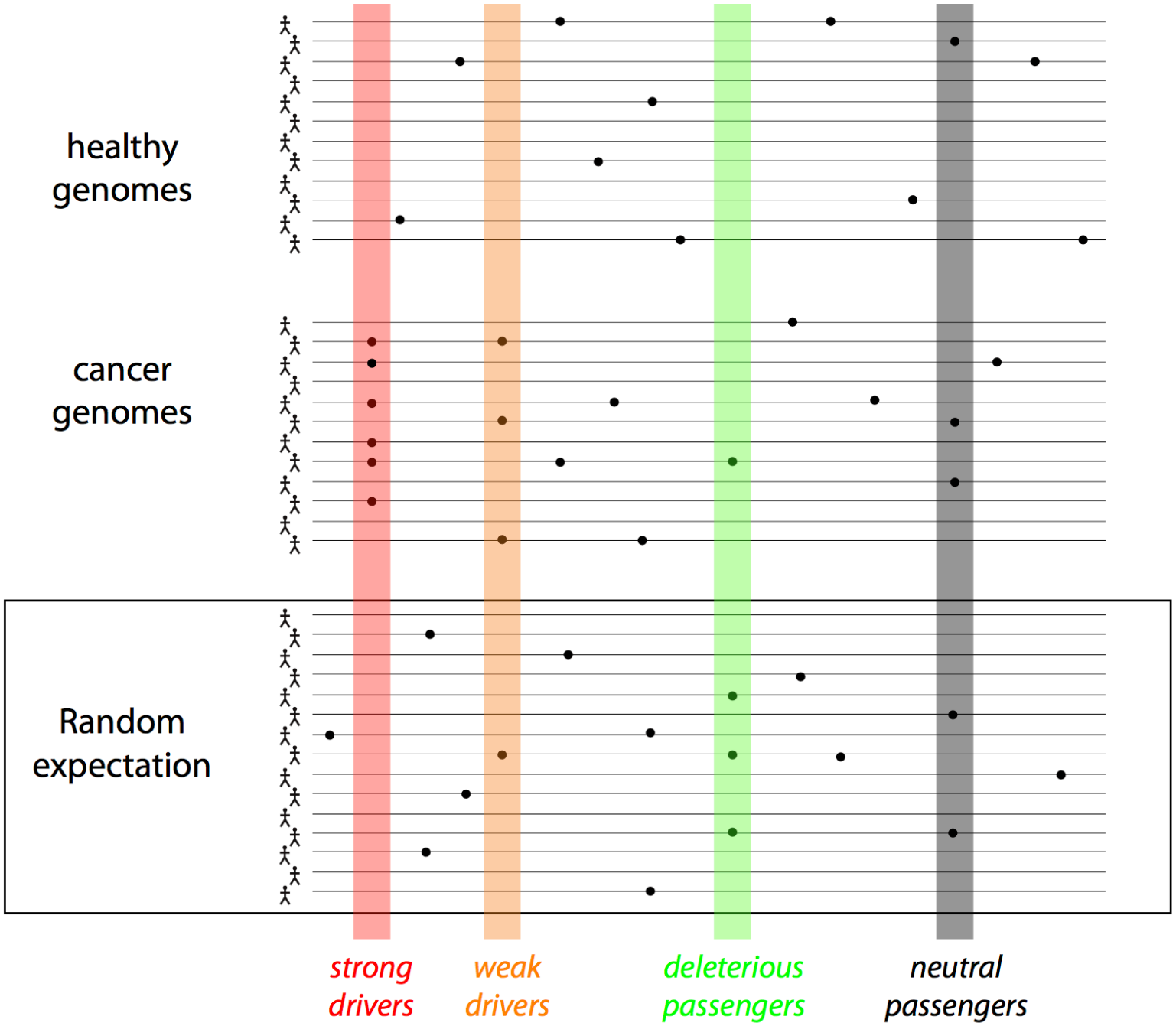
Cancer drivers: Significance & identification



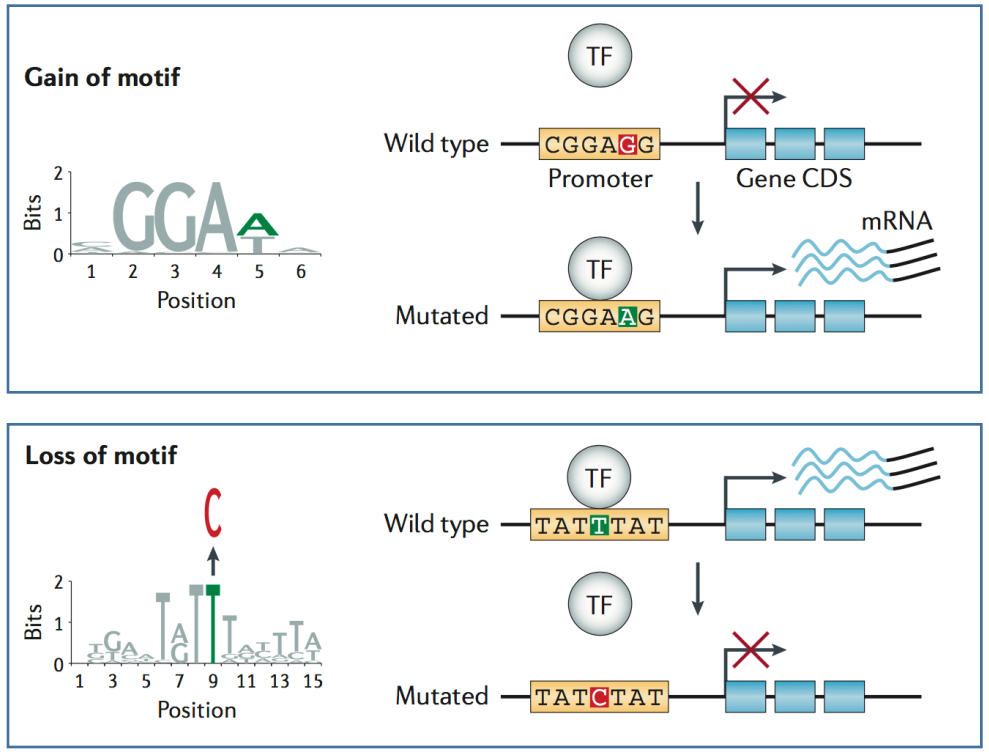
Yates et al, NRG (2012)

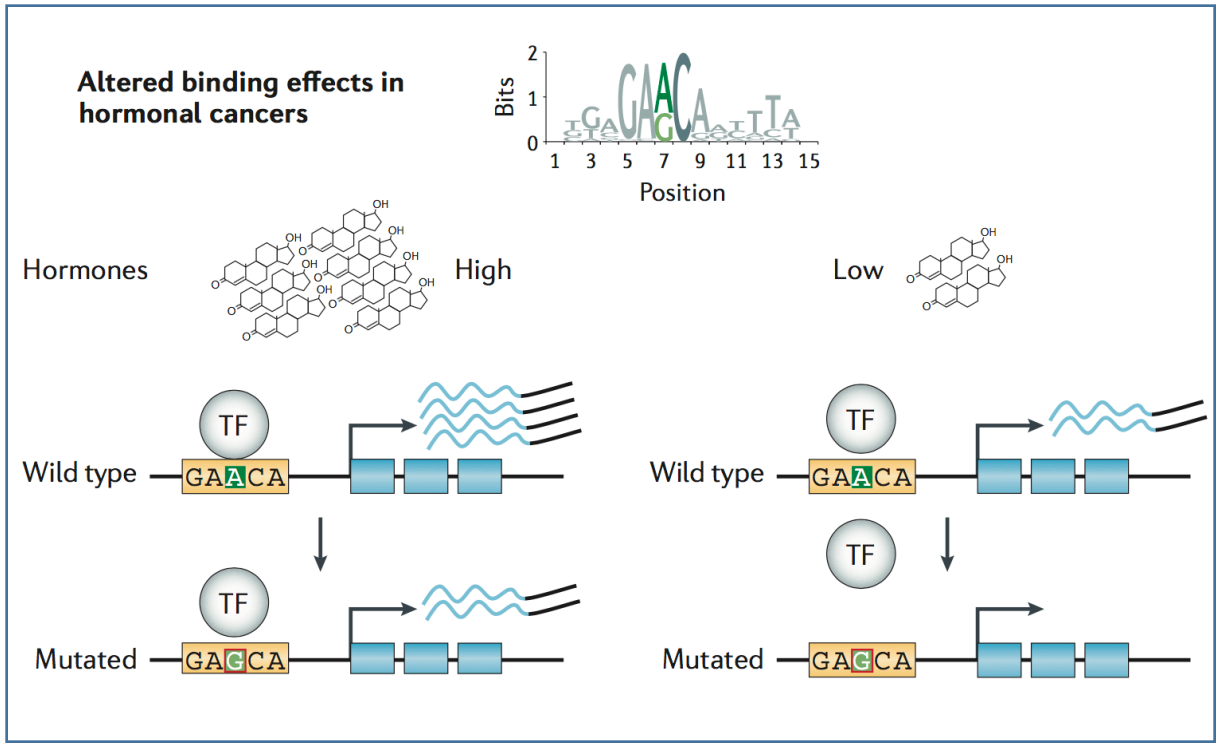

Functional Impact
weak
strong
common
rare
healthy genomes
(Population)
disease genomes

Cancer drivers: Significance & identification: frequency-based approaches



Cancer drivers: Significance & identification: functional annotations



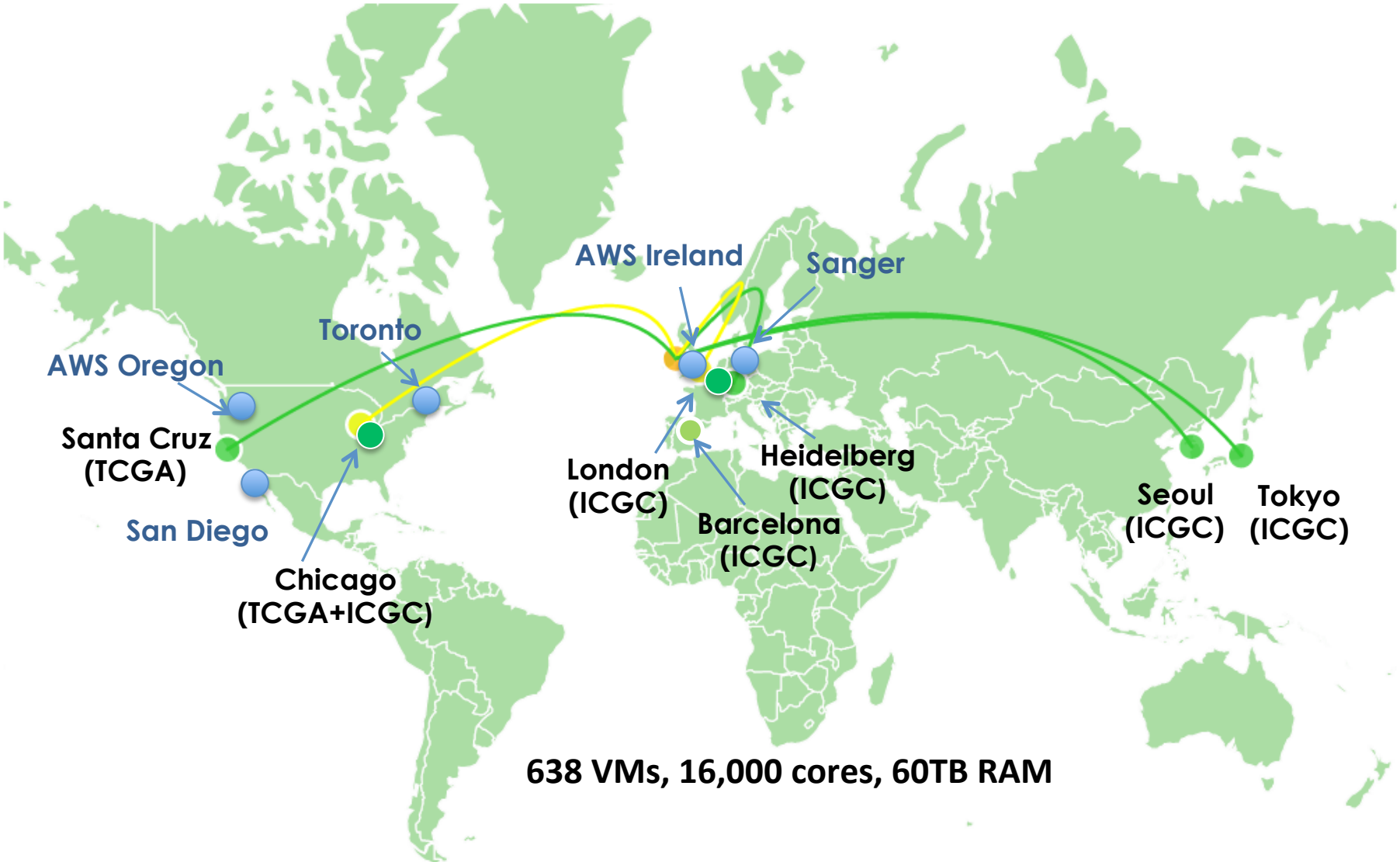


Khurana et al, NRG (2016)

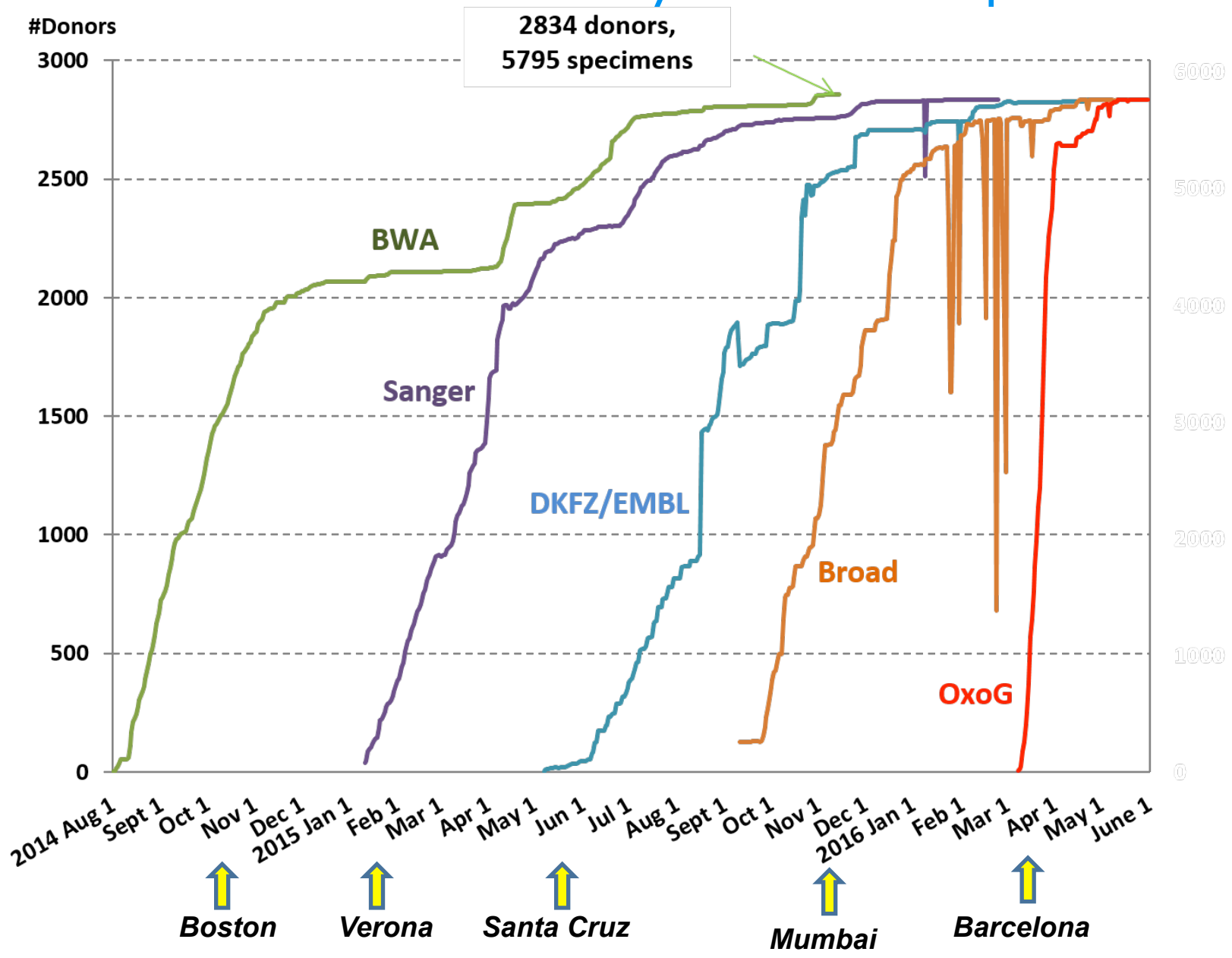
PCAWG
PanCancer Analysis
OF WHOLE GENOMES

- Goals:
  - Understand what's going on in the 95% of the cancer genome that isn't protein-coding.
    - Non-coding RNAs & regulatory elements
    - Genomic structural changes
    - Mutation signatures
    - Pathogen (viral) insertion
- Plan:
  - Jointly analyze 2600 whole genome tumor/normal pairs from ICGC.
  - >580 researchers
  - >130 research projects
  - 16 thematic working groups

PCAWG Data Processing

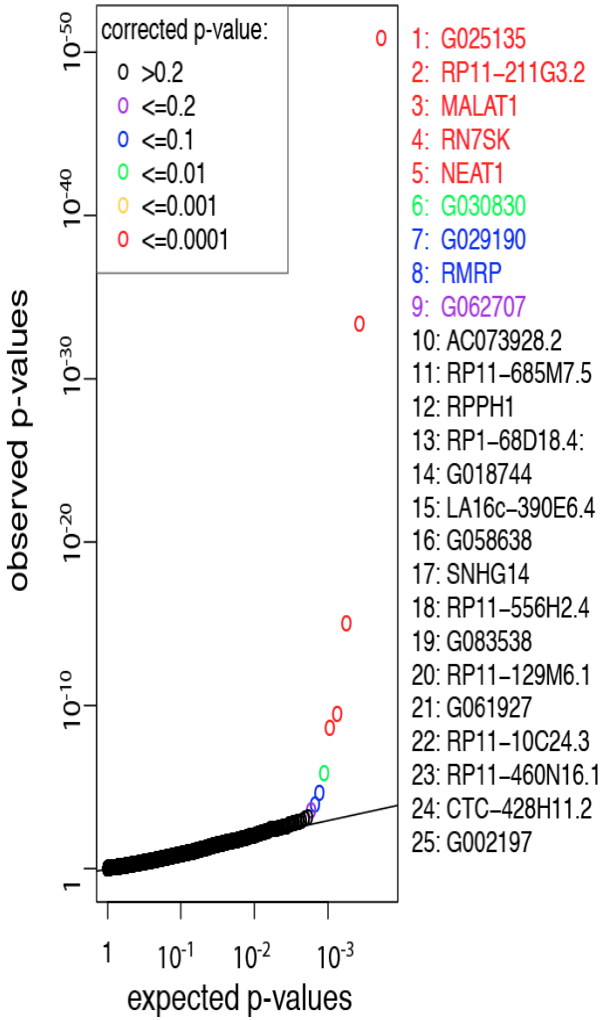


PCAWG Core Analyses Completed



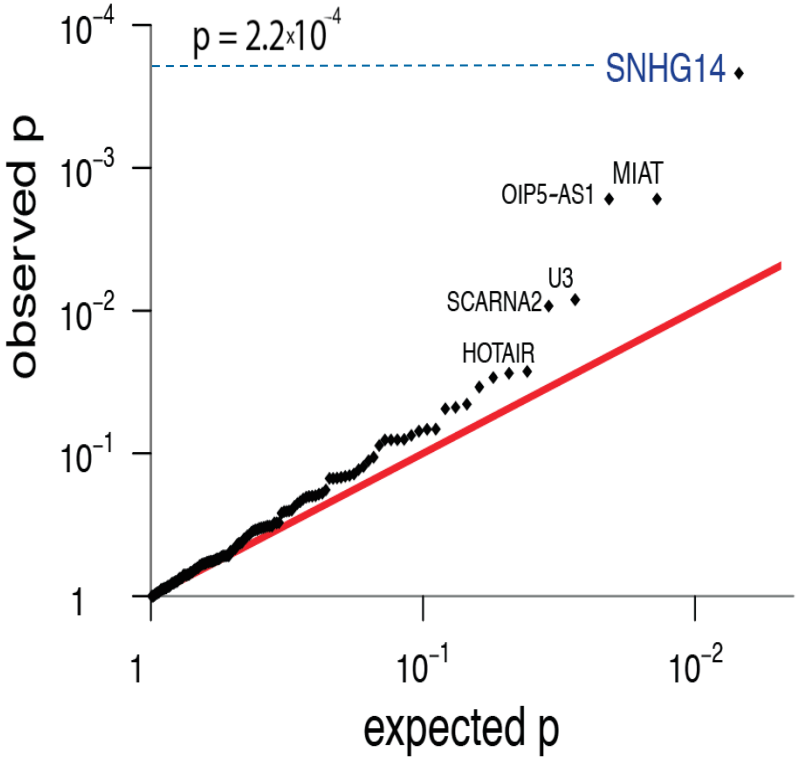
ncRNA driver candidates from PCAWG (preliminary)

Example lncRNA driver screen: ExInAtor - PANCAN excl. skin cancer

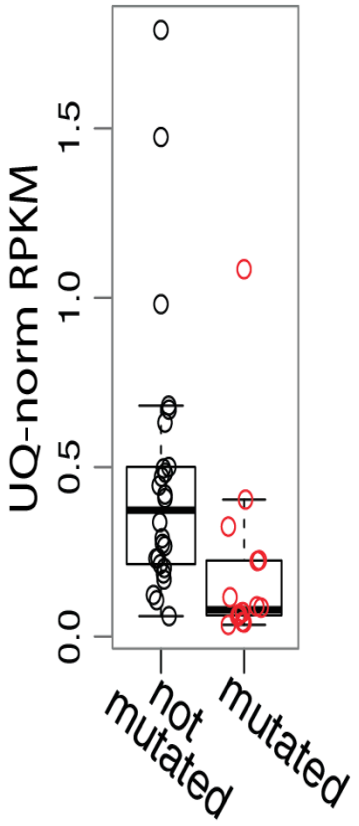


Andrés Lanzós and Rory Johnson (CRG, Barcelona)

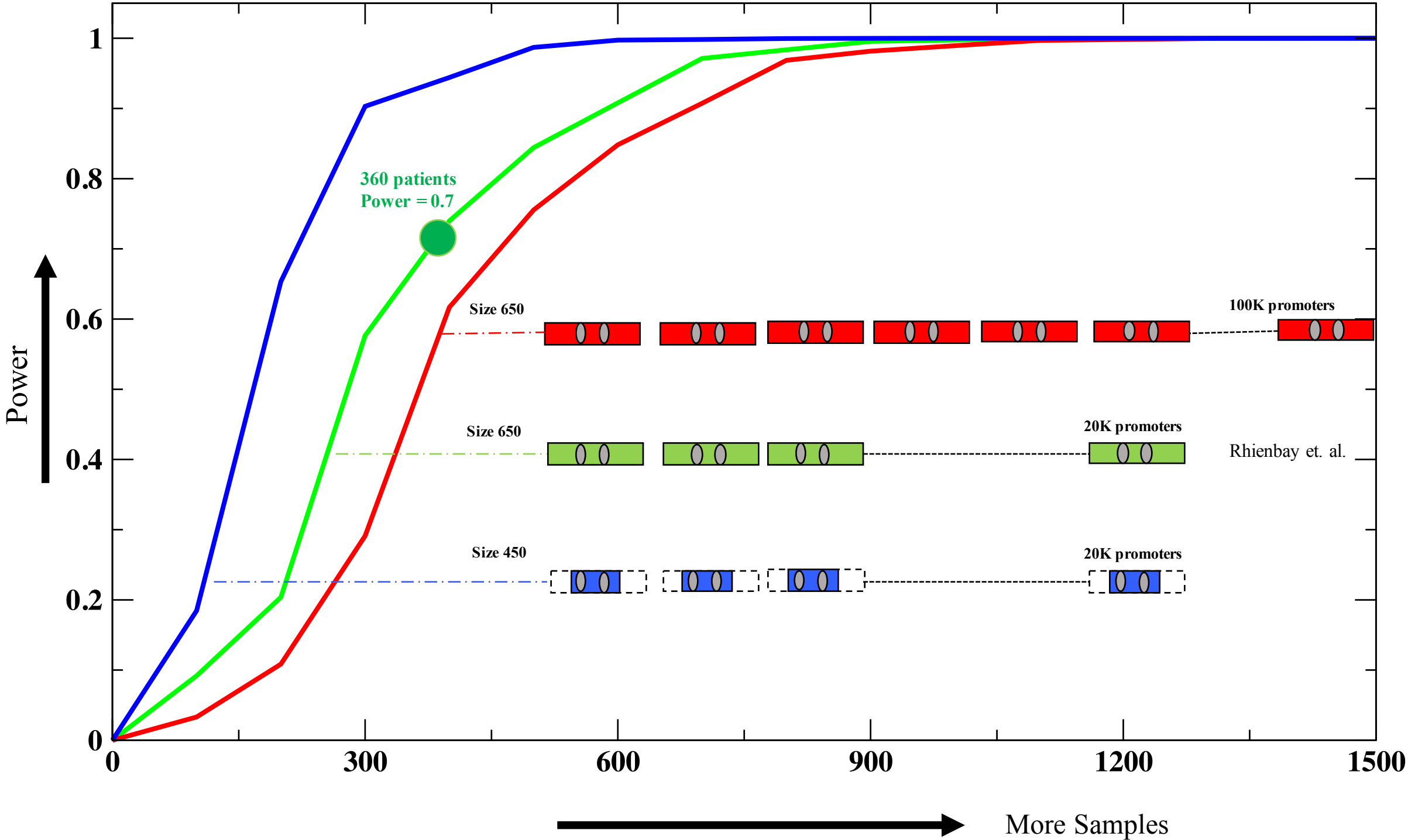
Example of mutation-to-expression correlation: Tier 1 lncRNAs (n=144) - colorectal



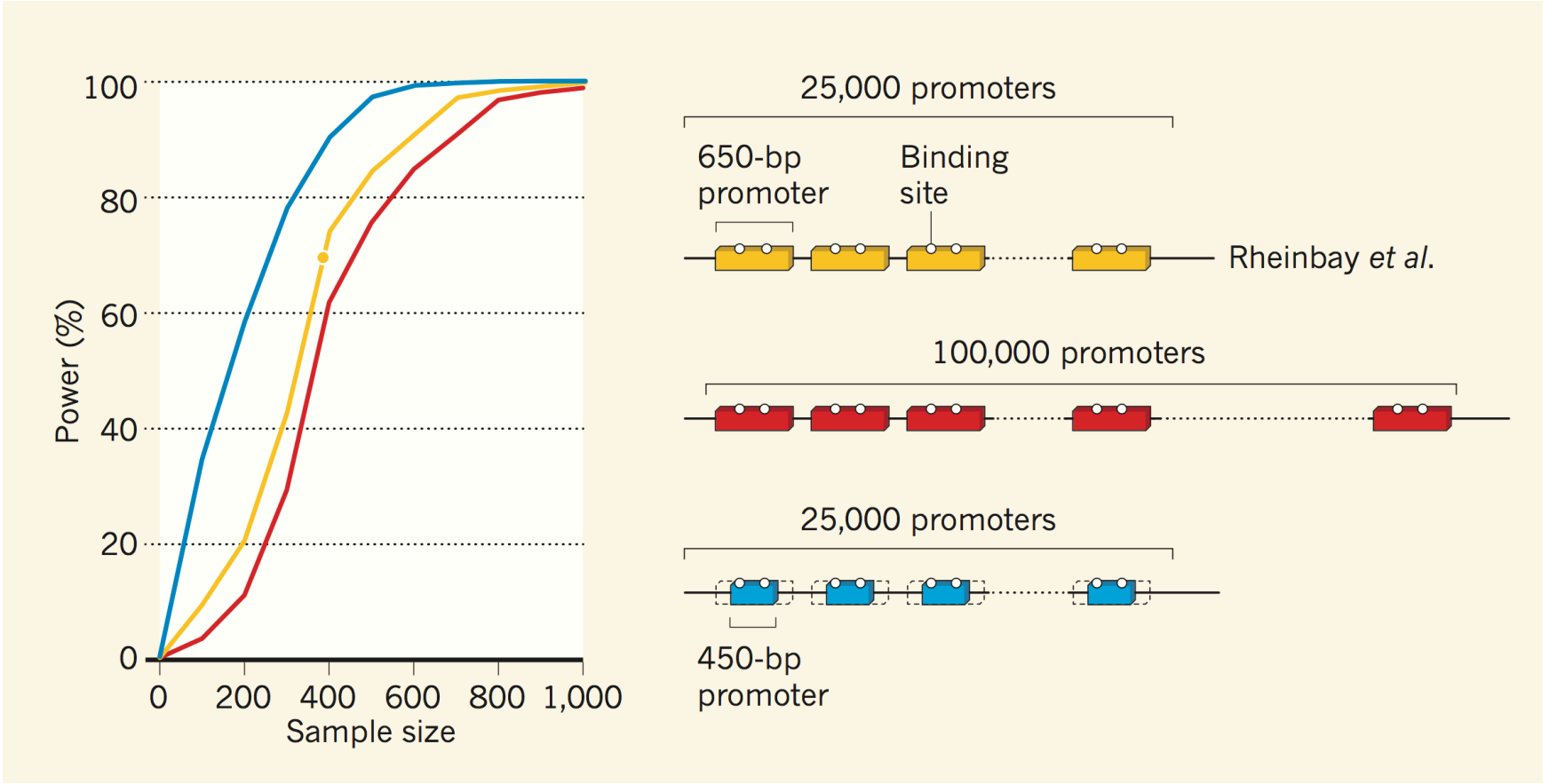
Small Nucleolar RNA Host Gene 14 (SNHG14)



Morten Muhlig Nielsen & Jakob Skou Pedersen (Aarhus University)


1
0.8
0.6
0.4
0.2
0
Power
0
300
600
900
1200
1500
360 patients
Power = 0.7
Size 650
100K promoters
Size 650
20K promoters
Rhienbay et. al.
Size 450
20K promoters
More Samples

Improving discovery of cancer-driving mutations in the non-coding genome



S. Kumar & M. Gerstein, Nature (2017)