

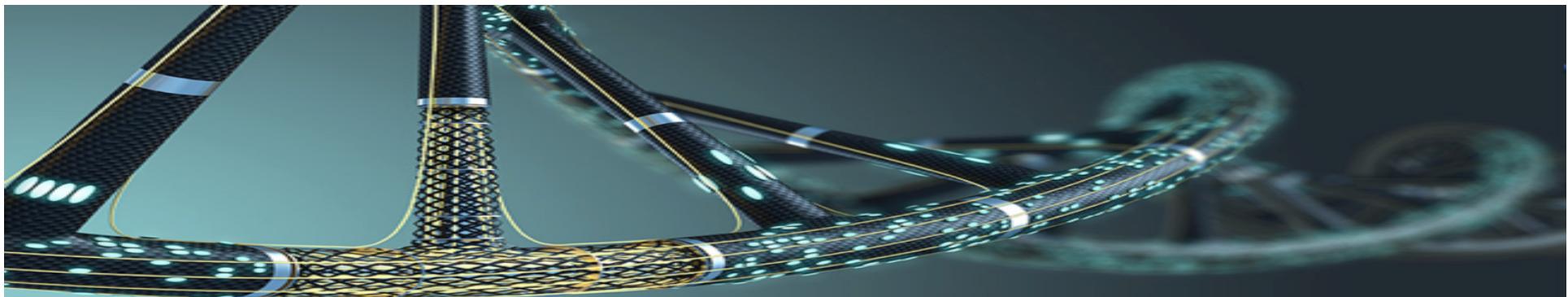


# Майнер по биоинформатике

Семестр 2

## Лекция 7

# Мария Попцова



# Single Blood Test Screens for Eight Cancer Types

Science

REPORTS

Cite as: J. D. Cohen *et al.*, *Science* 10.1126/science.aar3247 (2018).

## Detection and localization of surgically resectable cancers with a multi-analyte blood test

Joshua D. Cohen,<sup>1,2,3,4,5</sup> Lu Li,<sup>6</sup> Yuxuan Wang,<sup>1,2,3,4</sup> Christopher Thoburn,<sup>3</sup> Bahman Afsari,<sup>7</sup> Ludmila Danilova,<sup>7</sup> Christopher Douville,<sup>1,2,3,4</sup> Ammar A. Javed,<sup>8</sup> Fay Wong,<sup>1,2,3,4</sup> Austin Mattox,<sup>1,2,3,4</sup> Ralph. H. Hruban,<sup>3,4,9</sup> Christopher L. Wolfgang,<sup>8</sup> Michael G. Goggins,<sup>3,4,9,10,11</sup> Marco Dal Molin,<sup>4</sup> Tian-Li Wang,<sup>3,9</sup> Richard Roden,<sup>3,9</sup> Alison P. Klein,<sup>3,4,12</sup> Janine Ptak,<sup>1,2,3,4</sup> Lisa Dobbyn,<sup>1,2,3,4</sup> Joy Schaefer,<sup>1,2,3,4</sup> Natalie Silliman,<sup>1,2,3,4</sup> Maria Popoli,<sup>1,2,3,4</sup> Joshua T. Vogelstein,<sup>13</sup> James D. Browne,<sup>14</sup> Robert E. Schoen,<sup>15,16</sup> Randall E. Brand,<sup>15</sup> Jeanne Tie,<sup>17,18,19,20</sup> Peter Gibbs,<sup>17,18,19,20</sup> Hui-Li Wong,<sup>17</sup> Aaron S. Mansfield,<sup>21</sup> Jin Jen,<sup>22</sup> Samir M. Hanash,<sup>23</sup> Massimo Falconi,<sup>24</sup> Peter J. Allen,<sup>25</sup> Shibin Zhou,<sup>1,3,4</sup> Chetan Bettlegowda,<sup>1,2,3,4</sup> Luis Diaz,<sup>1,3,4</sup> Cristian Tomasetti,<sup>3,6,7\*</sup> Kenneth W. Kinzler,<sup>1,3,4\*</sup> Bert Vogelstein,<sup>1,2,3,4\*</sup> Anne Marie Lennon,<sup>3,4,8,10,11\*</sup> Nickolas Papadopoulos<sup>1,3,4\*</sup>

## 16 genes

- NRAS
- CTNNB1
- PIK3CA
- FBXW7
- APC
- EGFR
- BRAF
- CDKN2A
- PTEN
- FGFR2
- HRAS
- KRAS
- AKT1
- TP53
- PPP2R1A
- GNAS

# Detecting Cancers Earlier Through Elective Plasma-based CancerSEEK Testing

## Study Design

Go to

Study Type 1 : Observational

Estimated Enrollment 1 : 3000 participants

Observational Model: Cohort

Time Perspective: Prospective

Official Title: Detecting Cancers Earlier Through Elective Plasma-based CancerSEEK Testing - Ascertaining Serial Cancer Patients to Enable New Diagnostic

Actual Study Start Date 1 : November 18, 2019

Estimated Primary Completion Date 1 : April 20, 2020

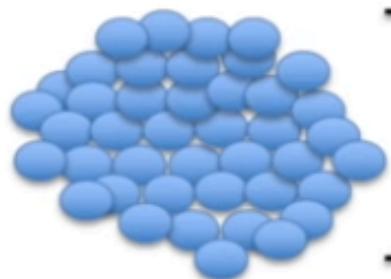
Estimated Study Completion Date 1 : June 30, 2020

This is a prospective, observational study of 1,000 subjects with known or suspected cancer confirmed through pathology reports and/or clinical/radiographic data and 2,000 subjects with no known cancer. De-identified blood samples and clinical data will be collected from subjects to validate a classification algorithm for a new version of the CancerSEEK assay.

<https://clinicaltrials.gov/ct2/show/NCT04213326>



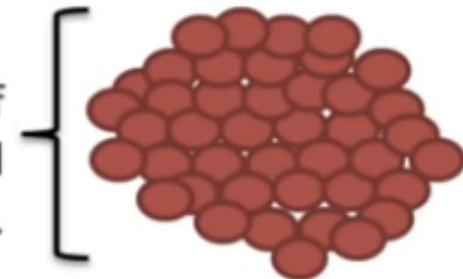
= a normal neural cell



A bunch of  
normal neural  
cells.



= a mutated neural cell



A bunch of  
mutated  
neural cells.

**The mutated cells behave differently than the normal cells.**

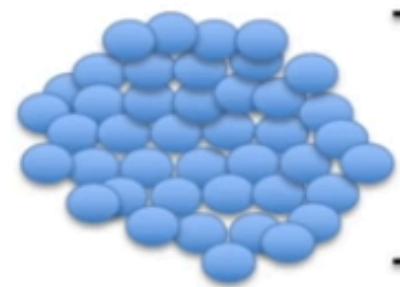
**We want to know what genetic mechanism is causing the difference...**

**This means we want to look at differences in gene expression.**



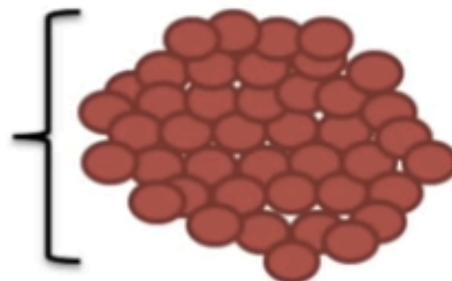
<https://www.youtube.com/watch?v=tlf6wYJrwKY>

● = a normal neural cell

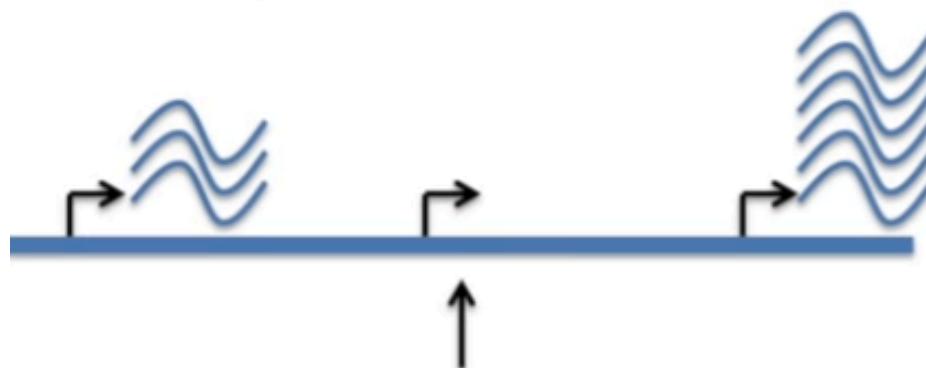


A bunch of  
normal neural  
cells.

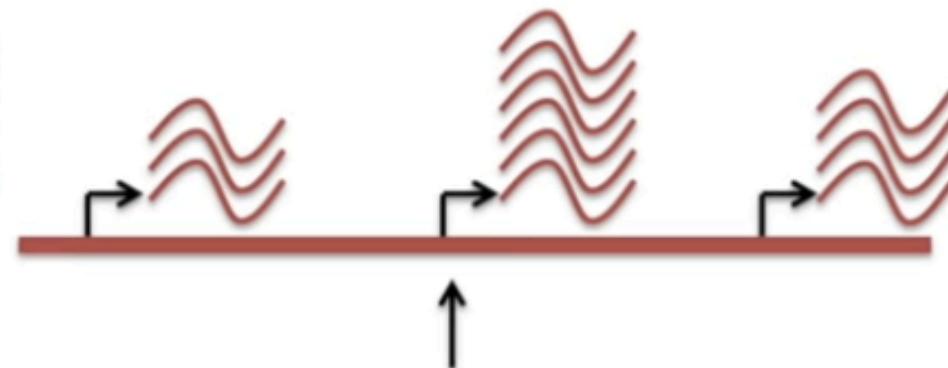
● = a mutated neural cell



A bunch of  
mutated  
neural cells.



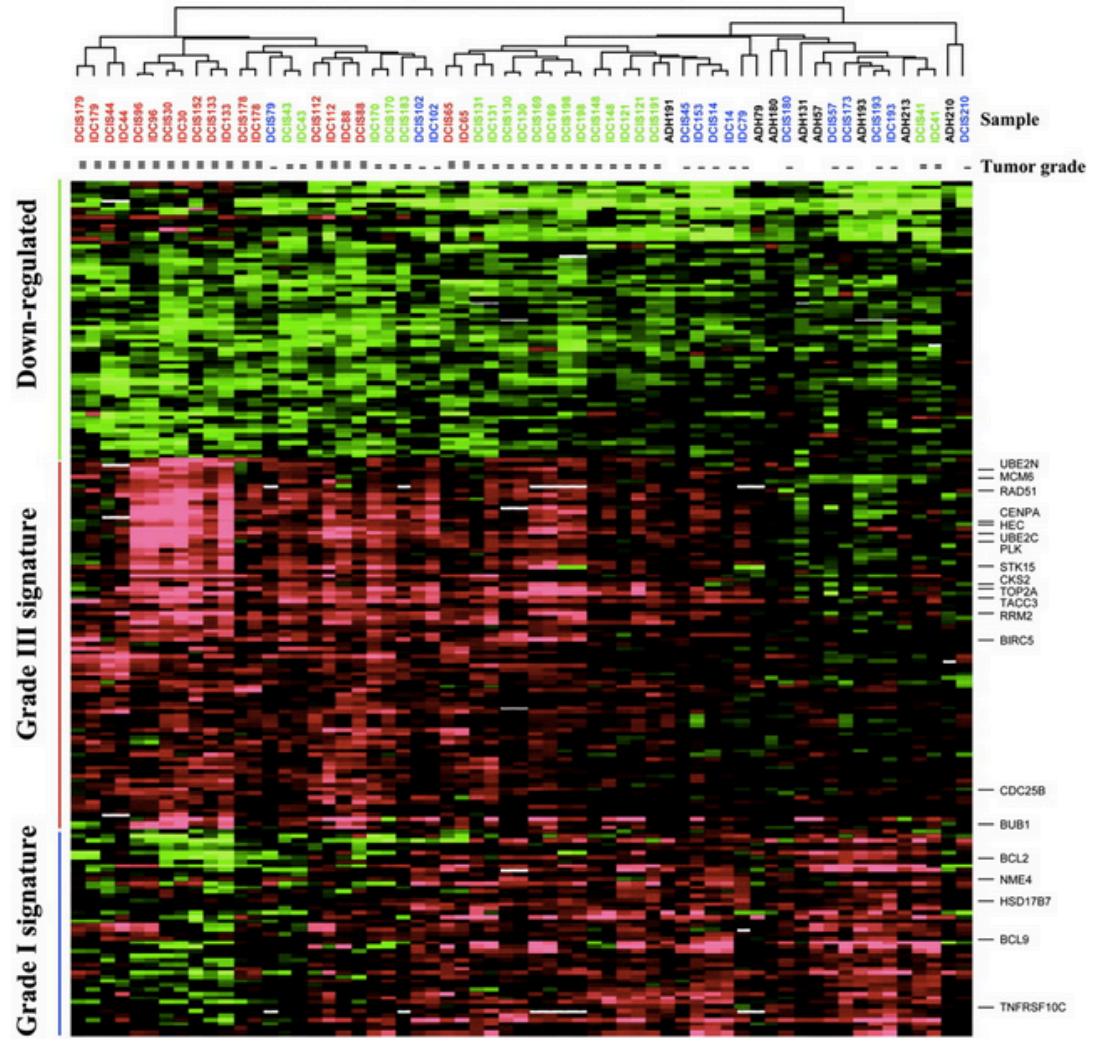
We can use RNA-seq to measure  
gene expression in normal cells...



... then use it to measure gene  
expression in mutated cells...

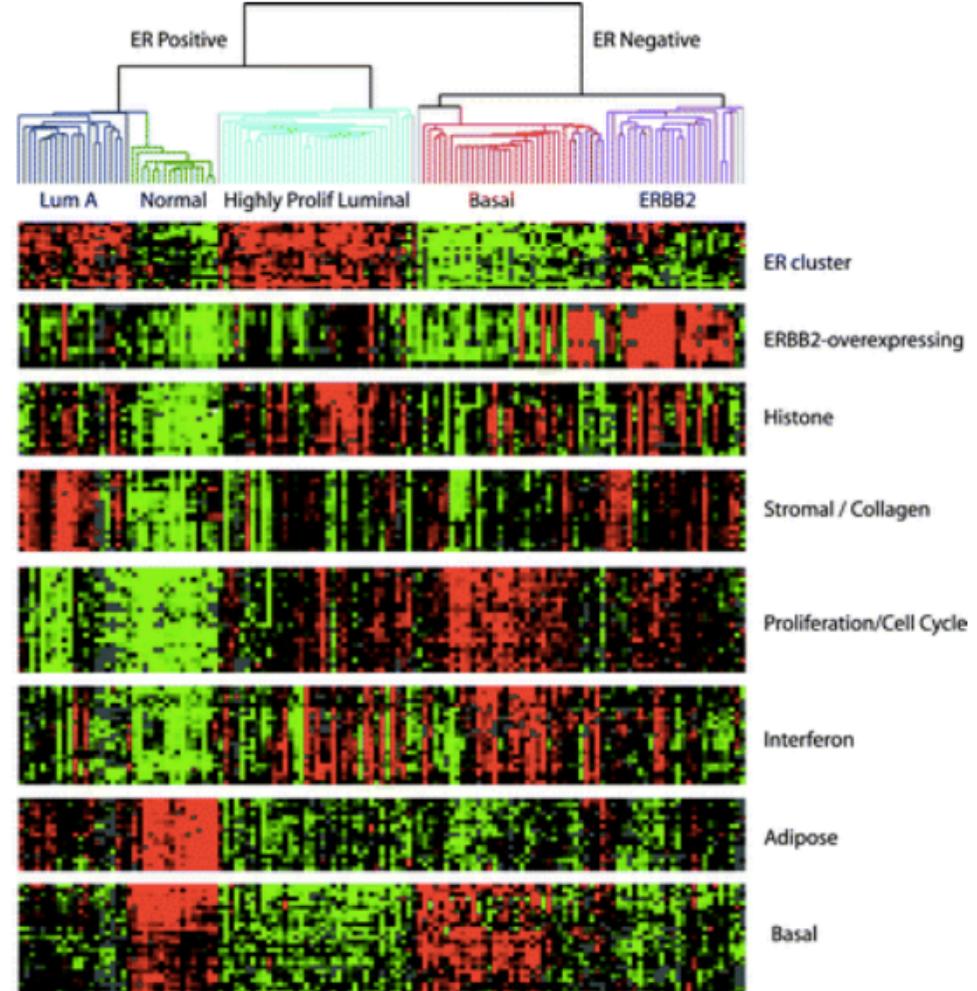
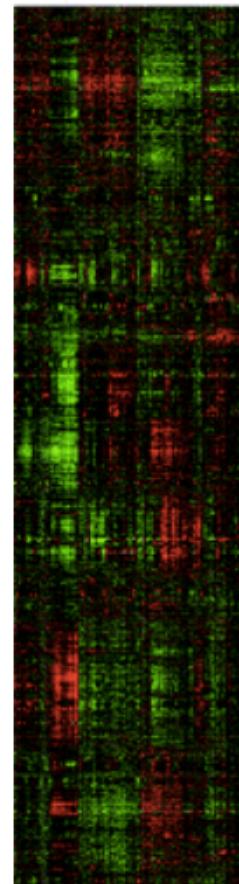


# Gene expression profiles of human breast cancer progression



# Transcriptomic signatures in breast cancer

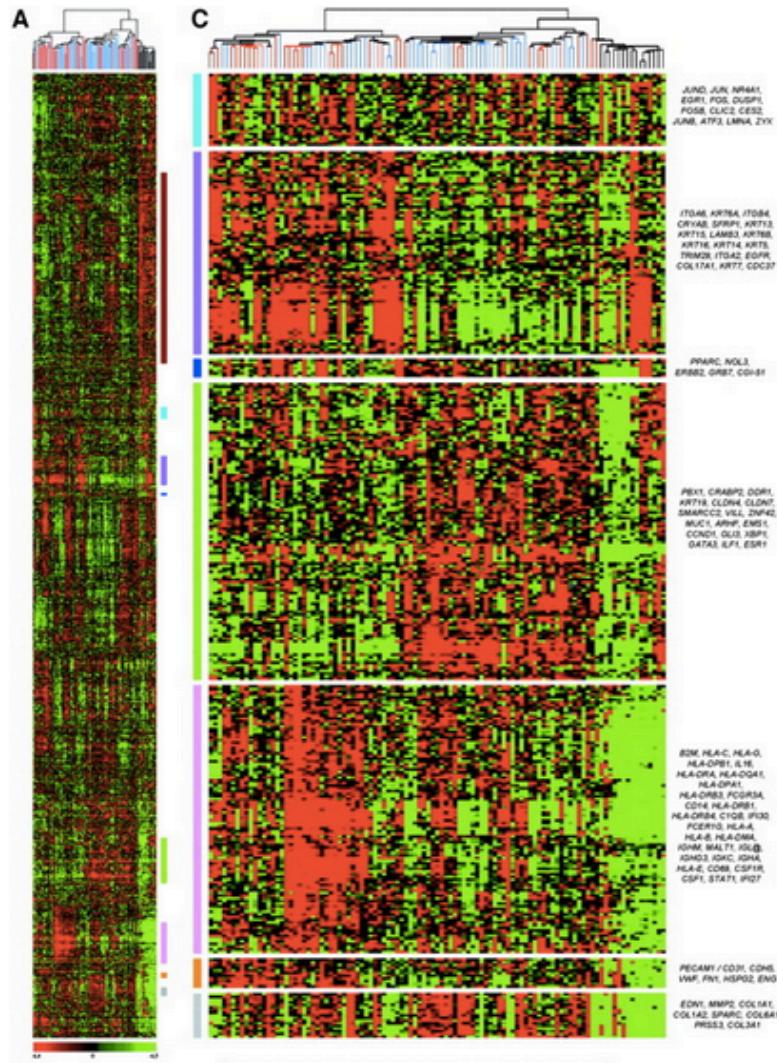
Expression profiles of 119 breast cancers and 16 normal tissues. Tumors cluster into defined molecular subtypes.



Jianjiang Fu and Stefanie S. Jeffrey  
Stanford University Medical Center

# Gene Expression Profiling for Molecular Characterization of Inflammatory Breast Cancer and Prediction of Response to Chemotherapy

Bertucci et al. Cancer Research 2004



Scientists now have an unprecedented view of the genetic changes that can contribute to cancers, such as squamous cell carcinoma, a common form of mouth cancer.



# Pan-cancer analysis of whole genomes

- Across the 2,583 white-listed PCAWG donors, we called 43,778,859 somatic SNVs, 410,123 somatic multinucleotide variants, 2,418,247 somatic indels, 288,416 somatic SVs, 19,166 somatic retrotransposition events and 8,185 de novo mitochondrial DNA mutations

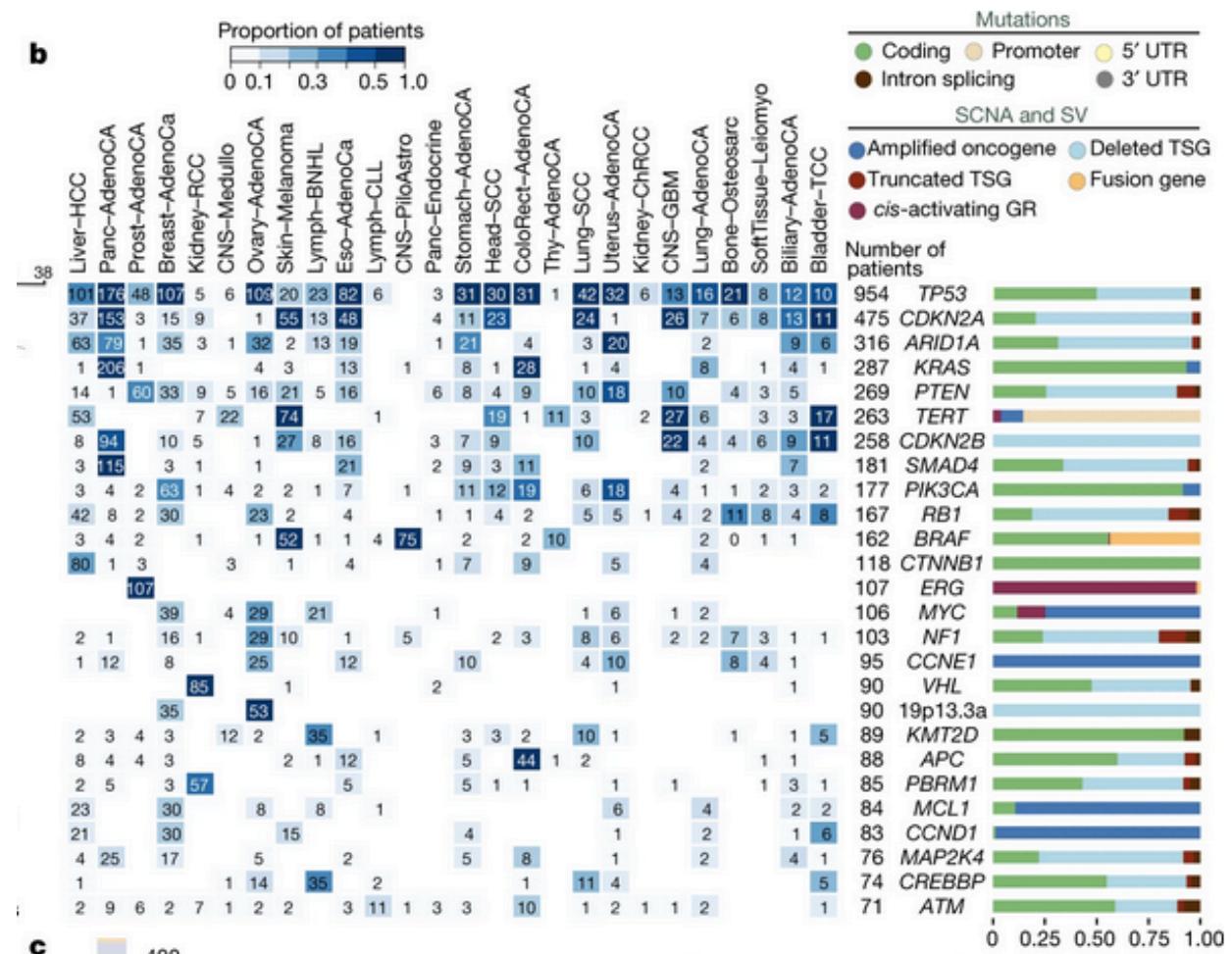
[The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium, Nature: 05 February 2020](#)

# Panorama of driver mutations in cancer

- On average, cancer genomes contained 4–5 driver mutations when combining coding and non-coding genomic elements; however, in around 5% of cases no drivers were identified, suggesting that cancer driver discovery is not yet complete.

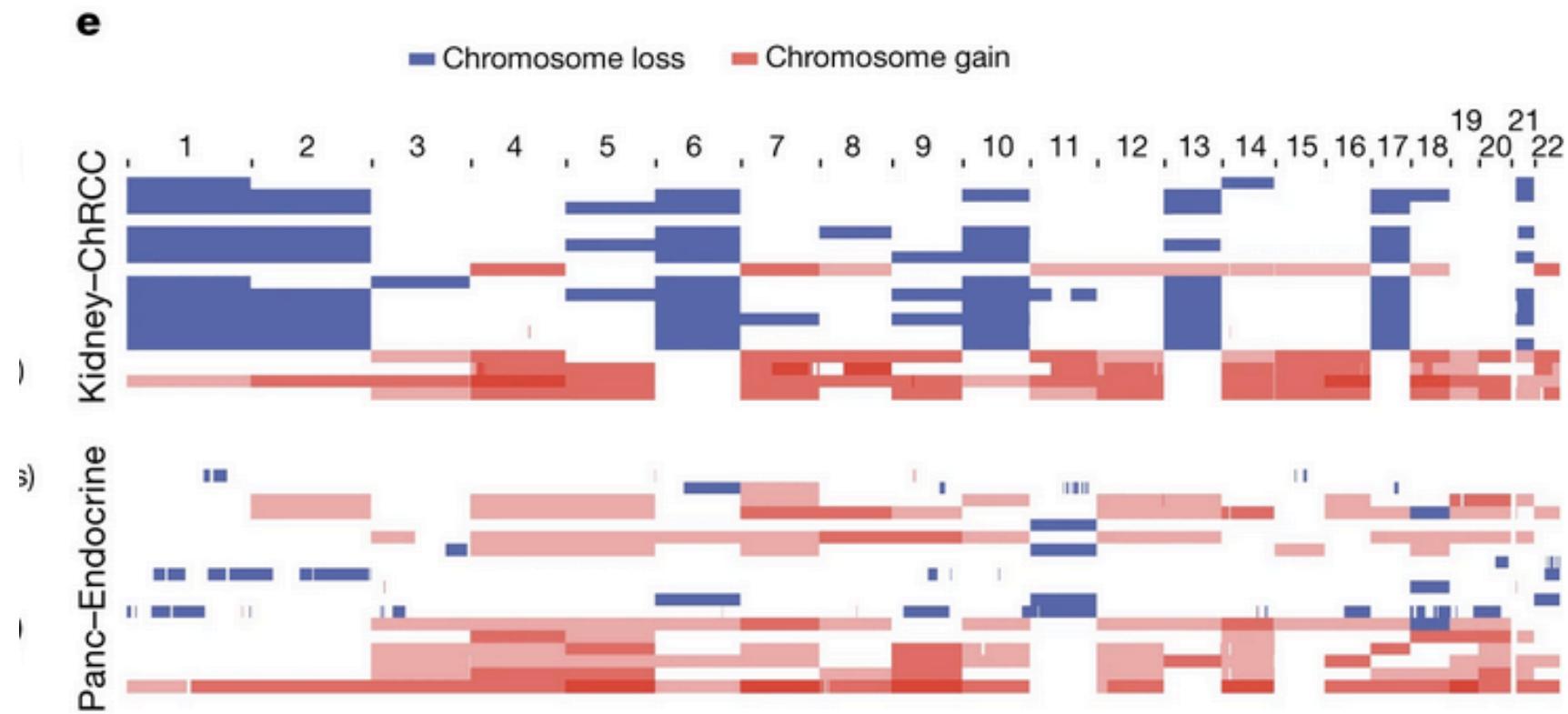
# ‘rank-and-cut’ approach to identify the probable drivers

- This approach works by ranking the observed mutations in a given genomic element based on recurrence, estimated functional consequence and expected pattern of drivers in that element.
- We then estimate the excess burden of somatic mutations in that genomic element above that expected for the background mutation rate, and cut the ranked mutations at this level.
- Mutations in each element with the highest driver ranking were then assigned as probable drivers; those below the threshold will probably have arisen through chance and were assigned as probable passengers.



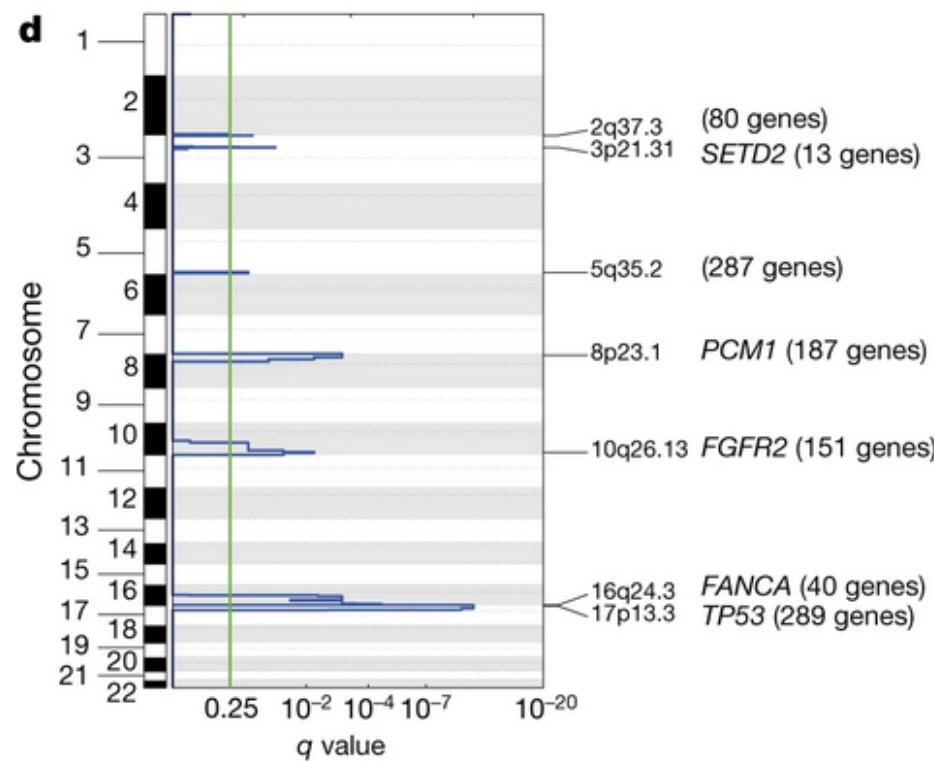
<https://www.nature.com/articles/s41586-020-1969-6/figures/2>

## Analysis of patients with no detected driver mutations



<https://www.nature.com/articles/s41586-020-1969-6/figures/3>

# Analysis of patients with no detected driver mutations.

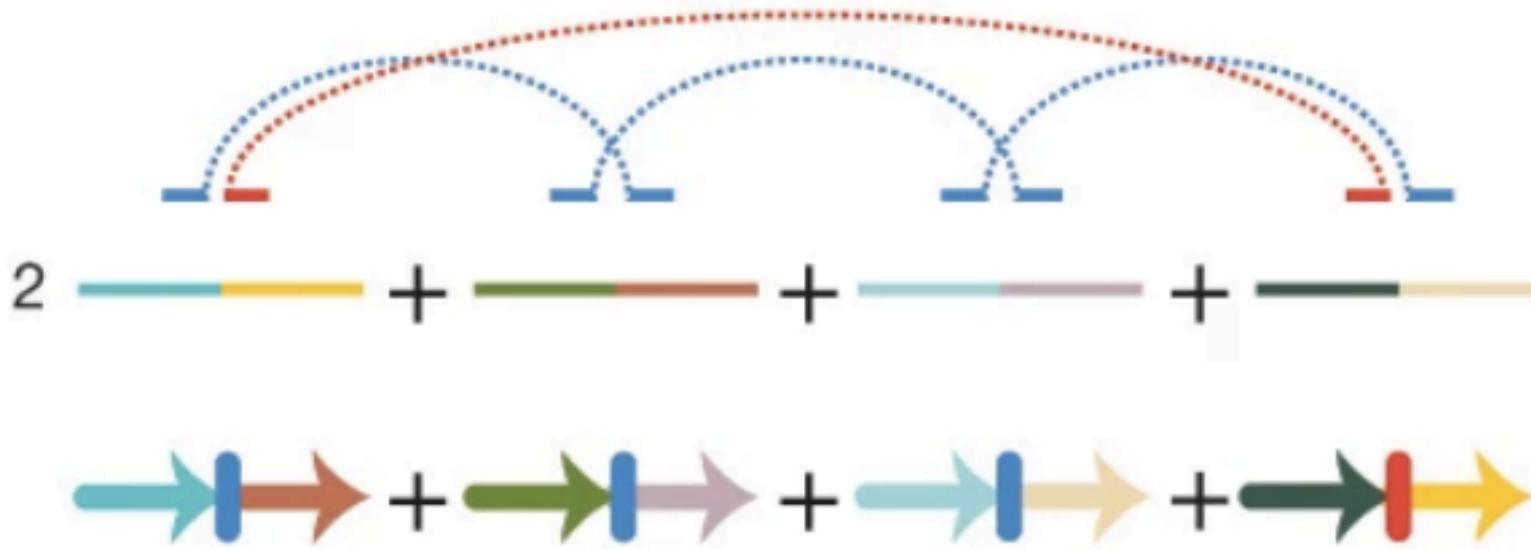


<https://www.nature.com/articles/s41586-020-1969-6/figures/3>

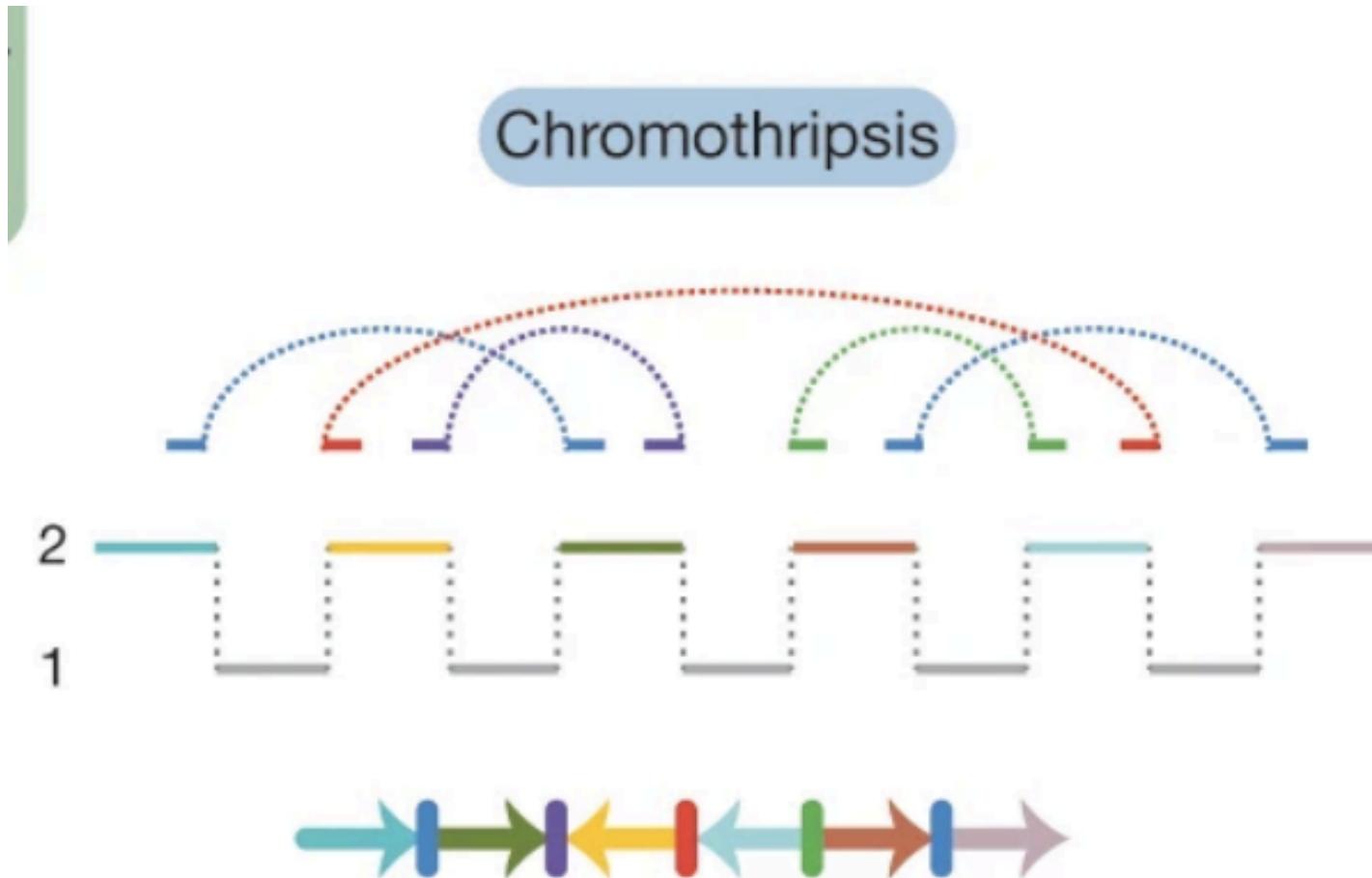
# Patterns of clustered mutations and SVs

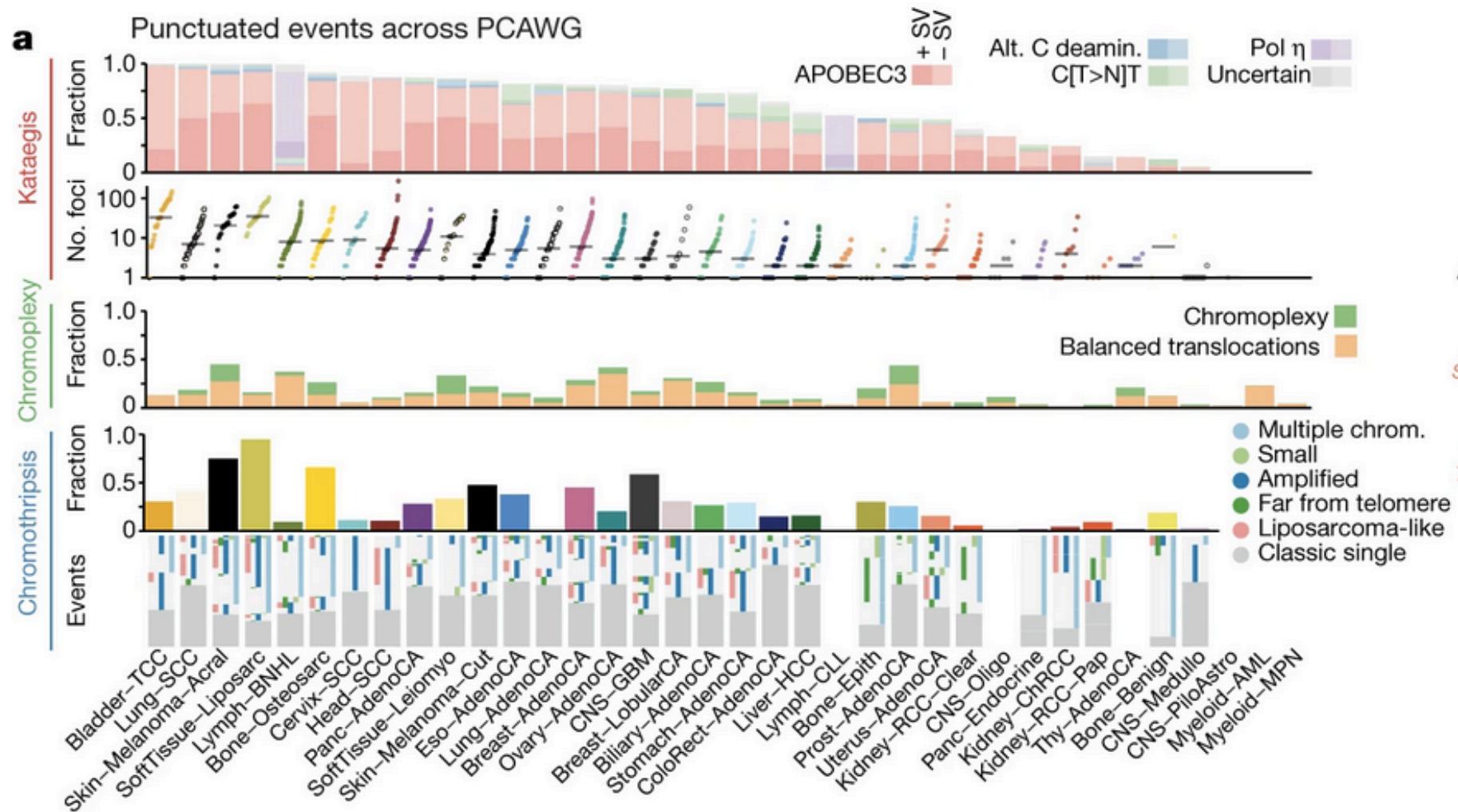
- 1) chromoplexy, in which repair of co-occurring double-stranded DNA breaks—typically on different chromosomes—results in shuffled chains of rearrangements;
- (2) kataegis, a focal hypermutation process that leads to locally clustered nucleotide substitutions, biased towards a single DNA strand
- (3) chromothripsis, in which tens to hundreds of DNA breaks occur simultaneously, clustered on one or a few chromosomes, with near-random stitching together of the resulting fragments

## Chromoplexy



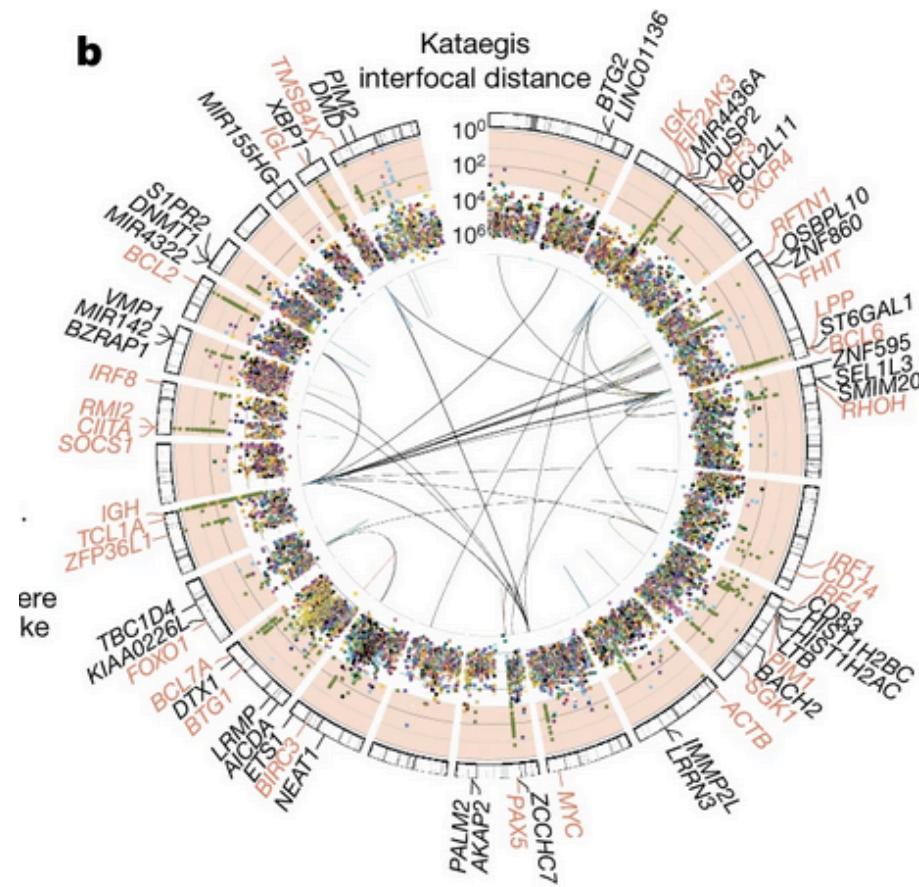
## Chromothripsis



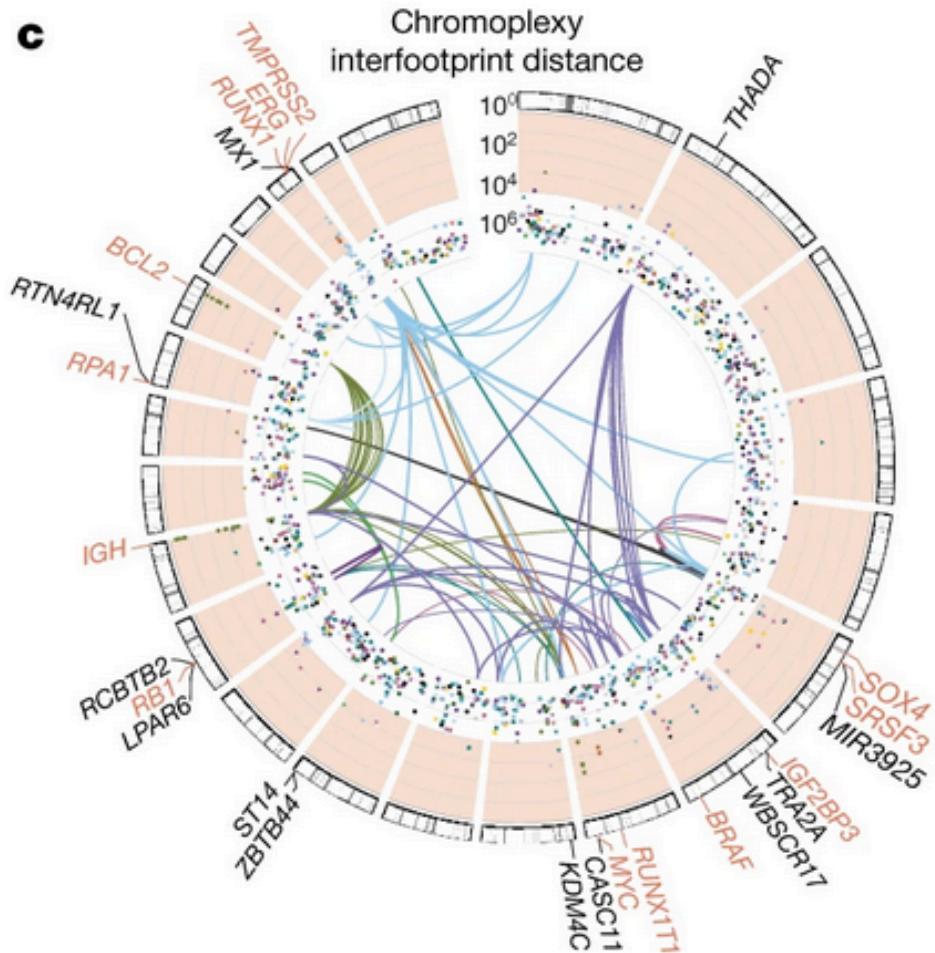


Circos rainfall plot showing the distances between consecutive kataegis events across PCAWG compared with their genomic position.

Lymphoid tumours (khaki, B cell non-Hodgkin's lymphoma; orange, chronic lymphocytic leukaemia) have hypermutation hot spots ( $\geq 3$  foci with distance  $\leq 1$  kb; pale red zone), many of which are near known cancer-associated genes (red annotations) and have associated SVs ( $\leq 10$  kb from the focus; shown as arcs in the centre)



Circos rainfall plot as in **b** that shows the distance versus the position of consecutive chromoplexy and reciprocal translocation footprints across PCAWG. Lymphoid, prostate and thyroid cancers exhibit recurrent events ( $\geq 2$  footprints with distance  $\leq 10$  kb; pale red zone) that are likely to be driver SVs and are annotated with nearby genes and associated SVs, which are shown as bold and thin arcs for chromoplexy and reciprocal translocations, respectively (colours as in **a**).

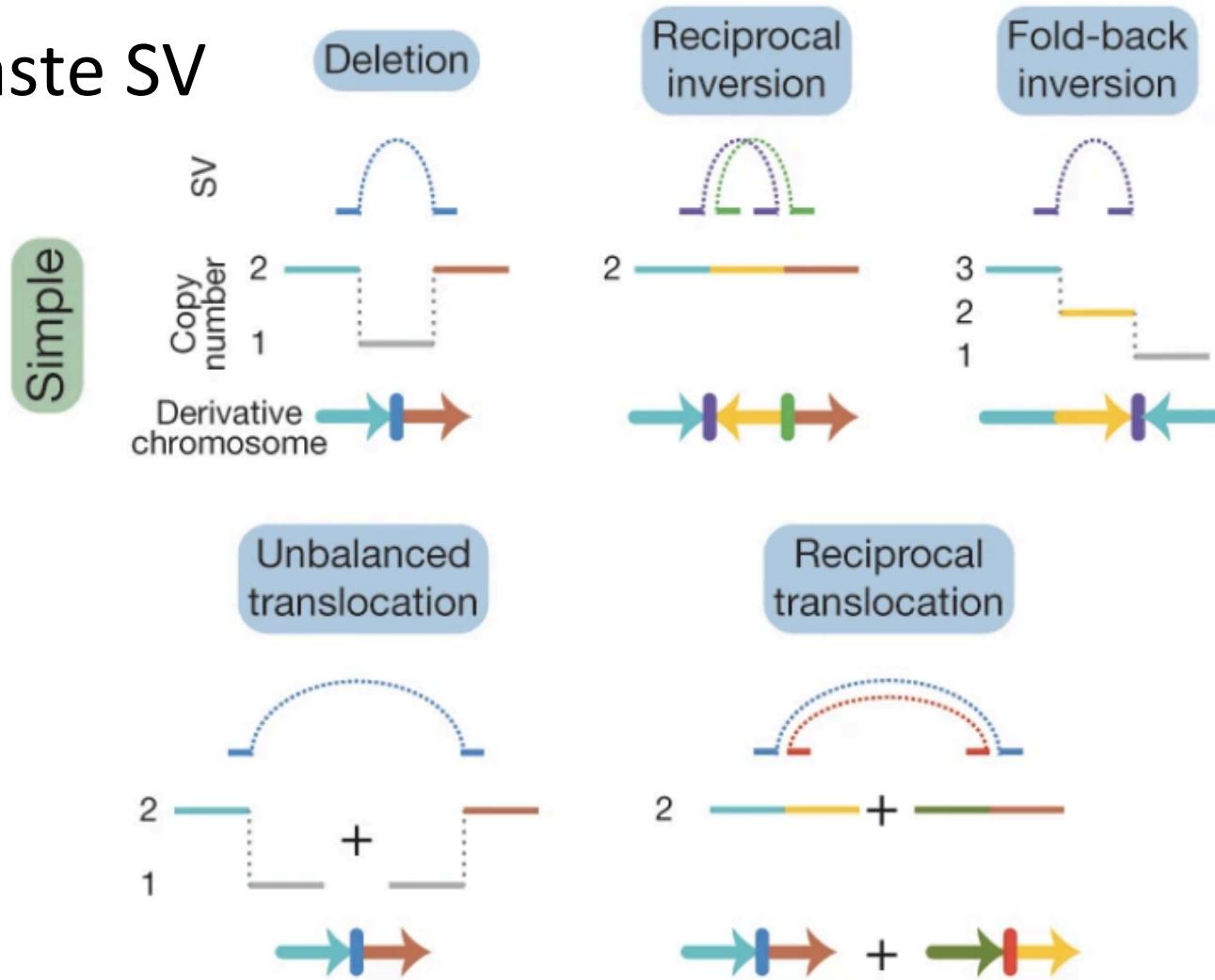


# **Patterns of somatic structural variation in human cancer genomes**

# **Classification of structural variants in cancer genomes**

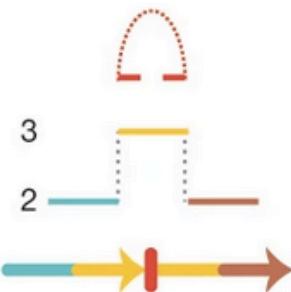
<https://www.nature.com/articles/s41586-019-1913-9/figures/1>

# Cut-and-paste SV

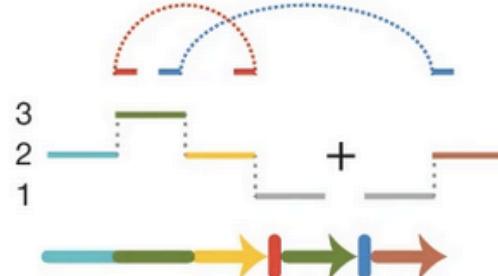


## Copy-and-paste SV

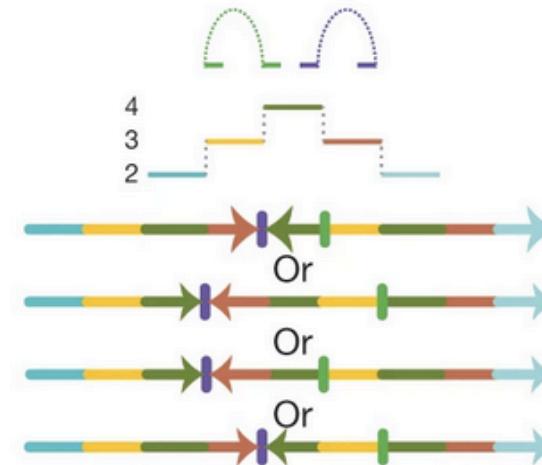
### Tandem duplication



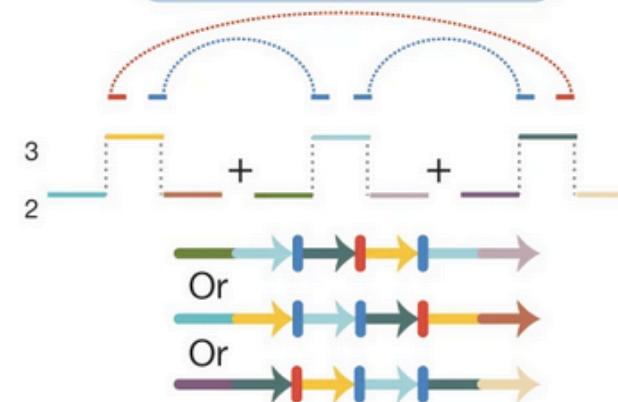
### Local-distant cluster



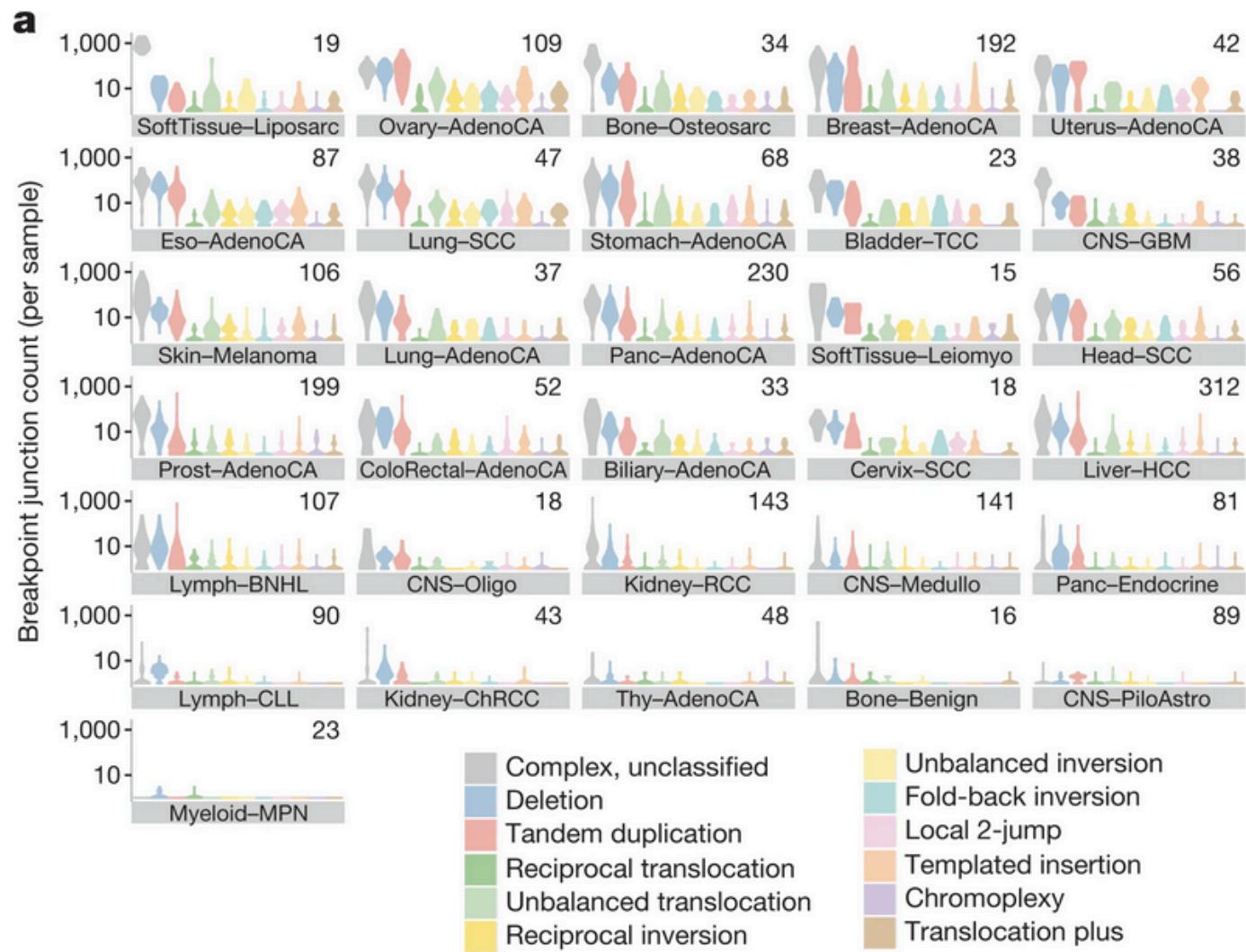
## Local $n$ -jump



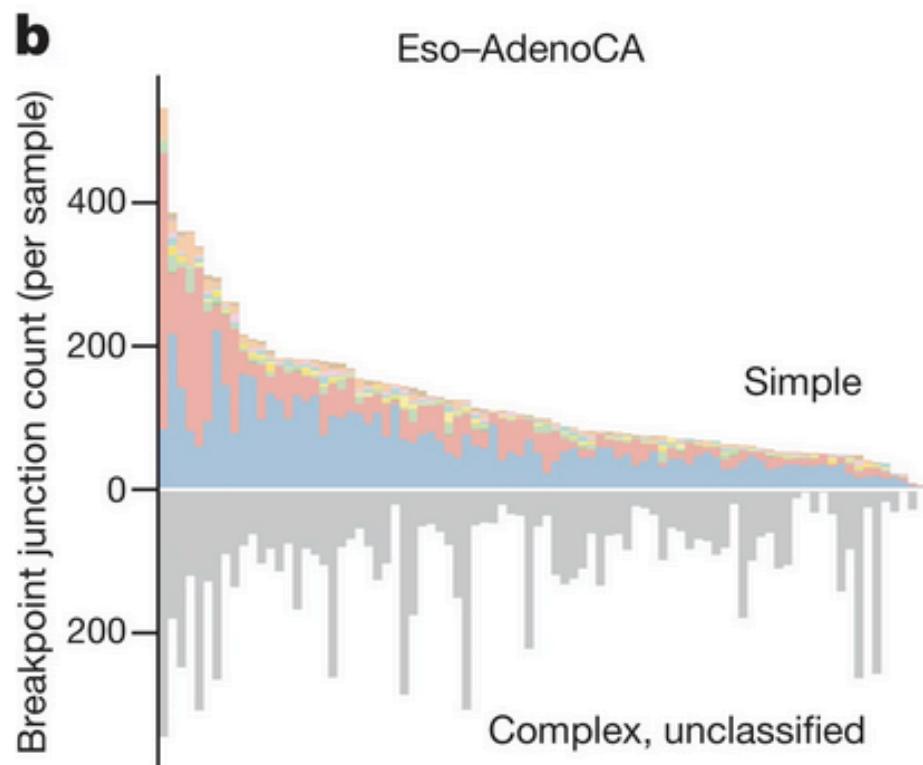
### Cycle of templated insertions



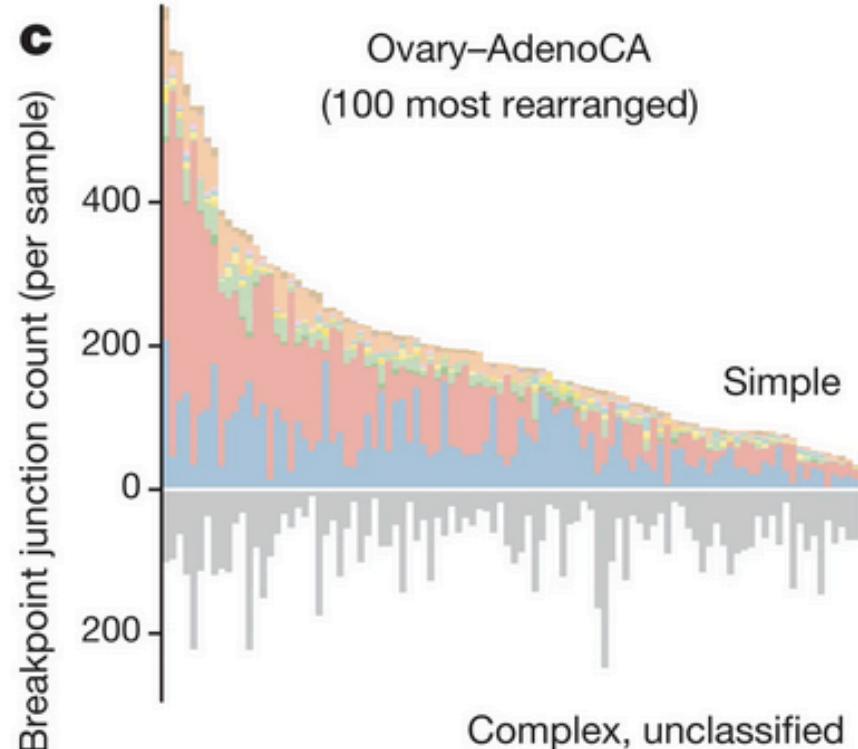
Violin plots of density of classified structural-variant categories across patients within each histology group.



Per-sample counts of complex (bottom) and classified (top) structural-variant breakpoint junctions for oesophageal adenocarcinoma.

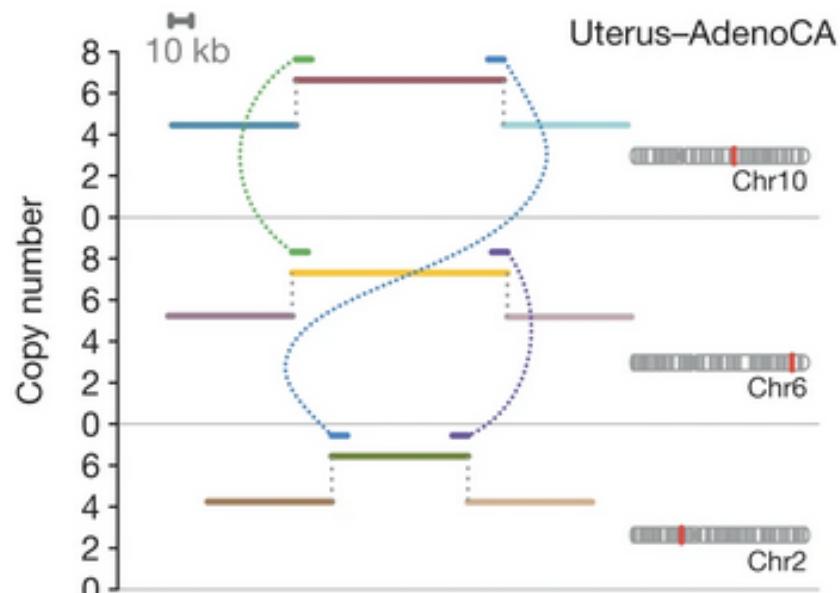


Per-sample counts of complex (bottom) and classified (top) structural-variant breakpoint junctions for ovarian adenocarcinoma.

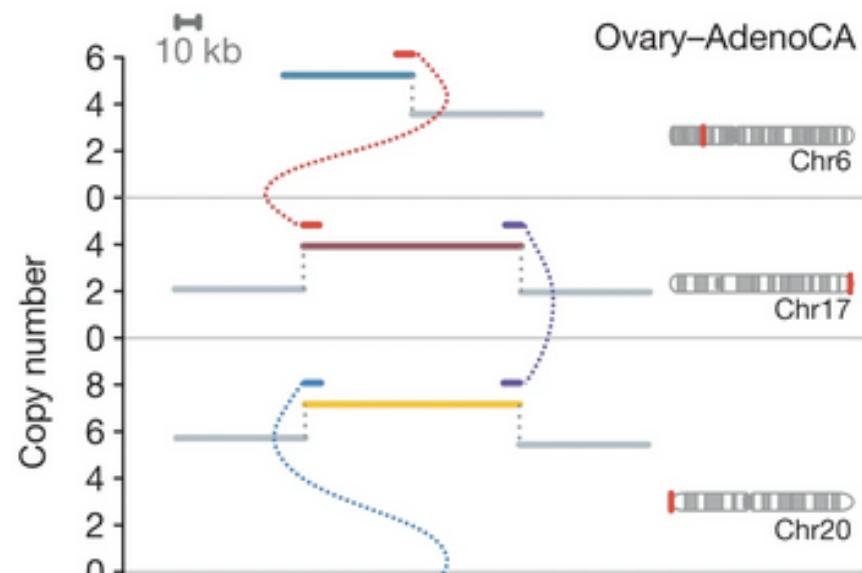


# **Chains, cycles and bridges of templated insertions.**

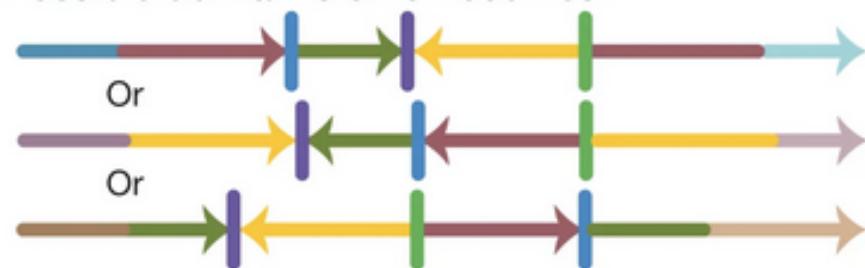
**a** Cycle of templated insertions

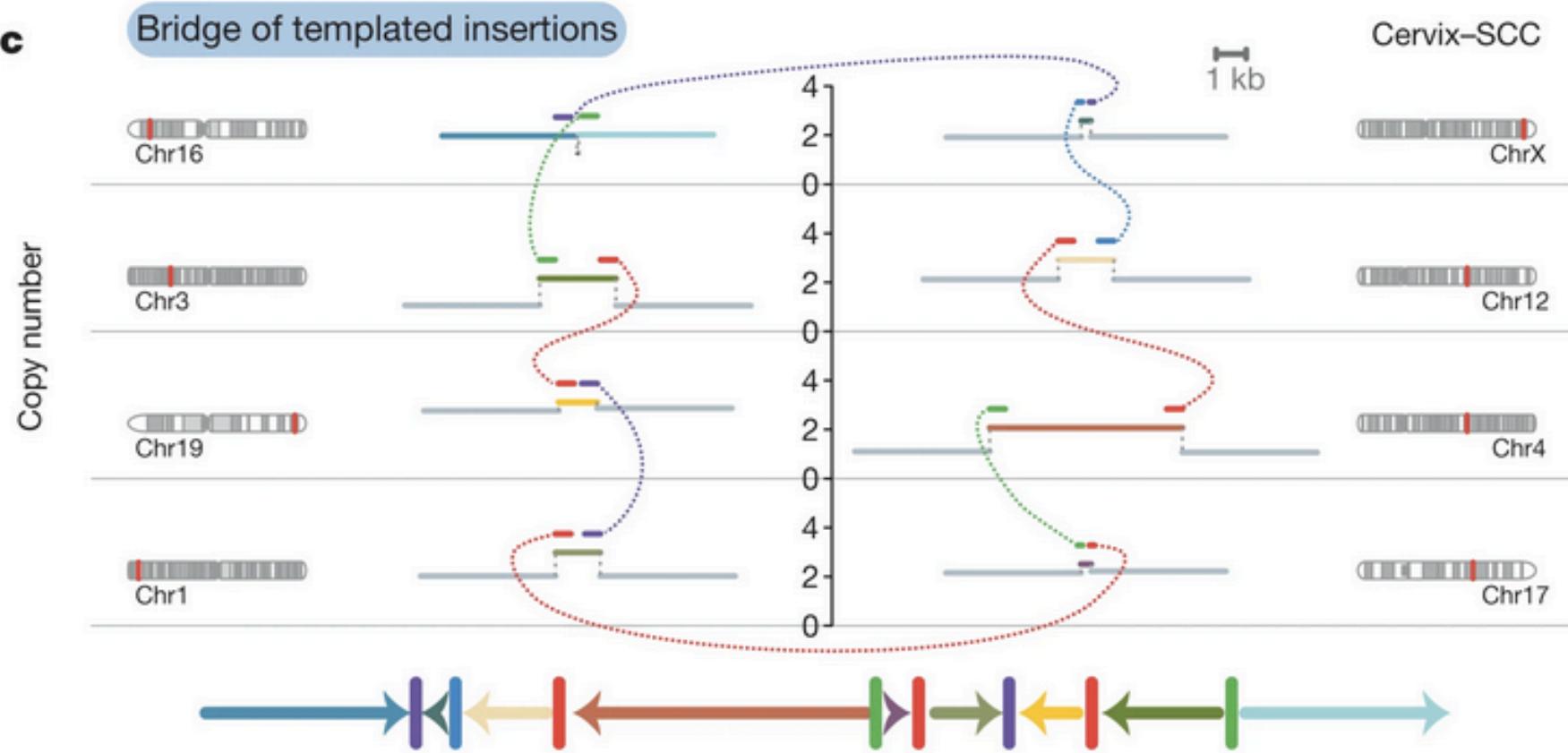


**b** Chain of templated insertions



Possible derivative chromosomes:



**c**

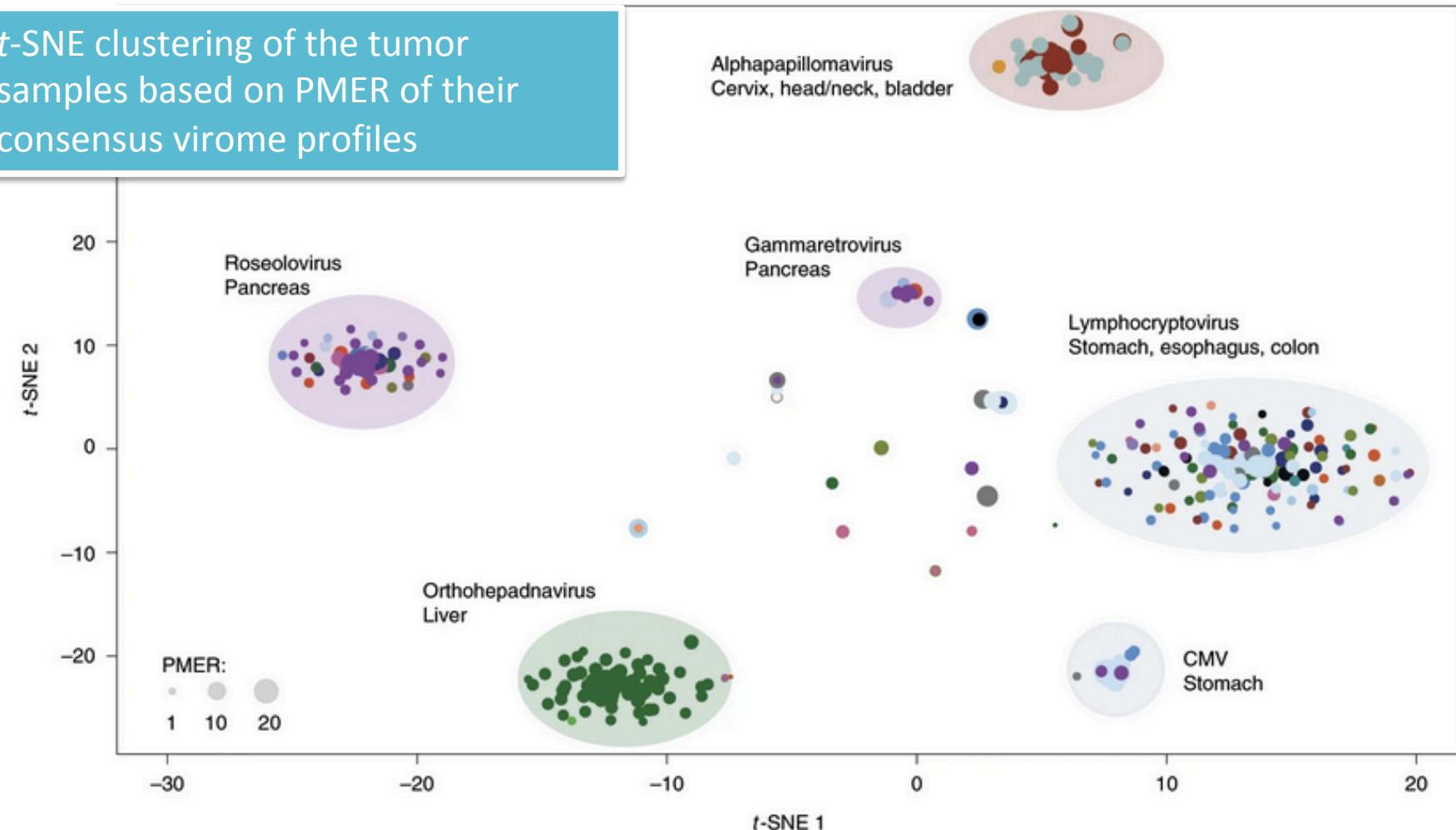
# The landscape of viral associations in human cancers

- Viruses were detected in 382 genome and 68 transcriptome datasets. We found a high prevalence of known tumor-associated viruses such as Epstein–Barr virus (EBV), hepatitis B virus (HBV) and human papilloma virus (HPV; for example, HPV16 or HPV18).

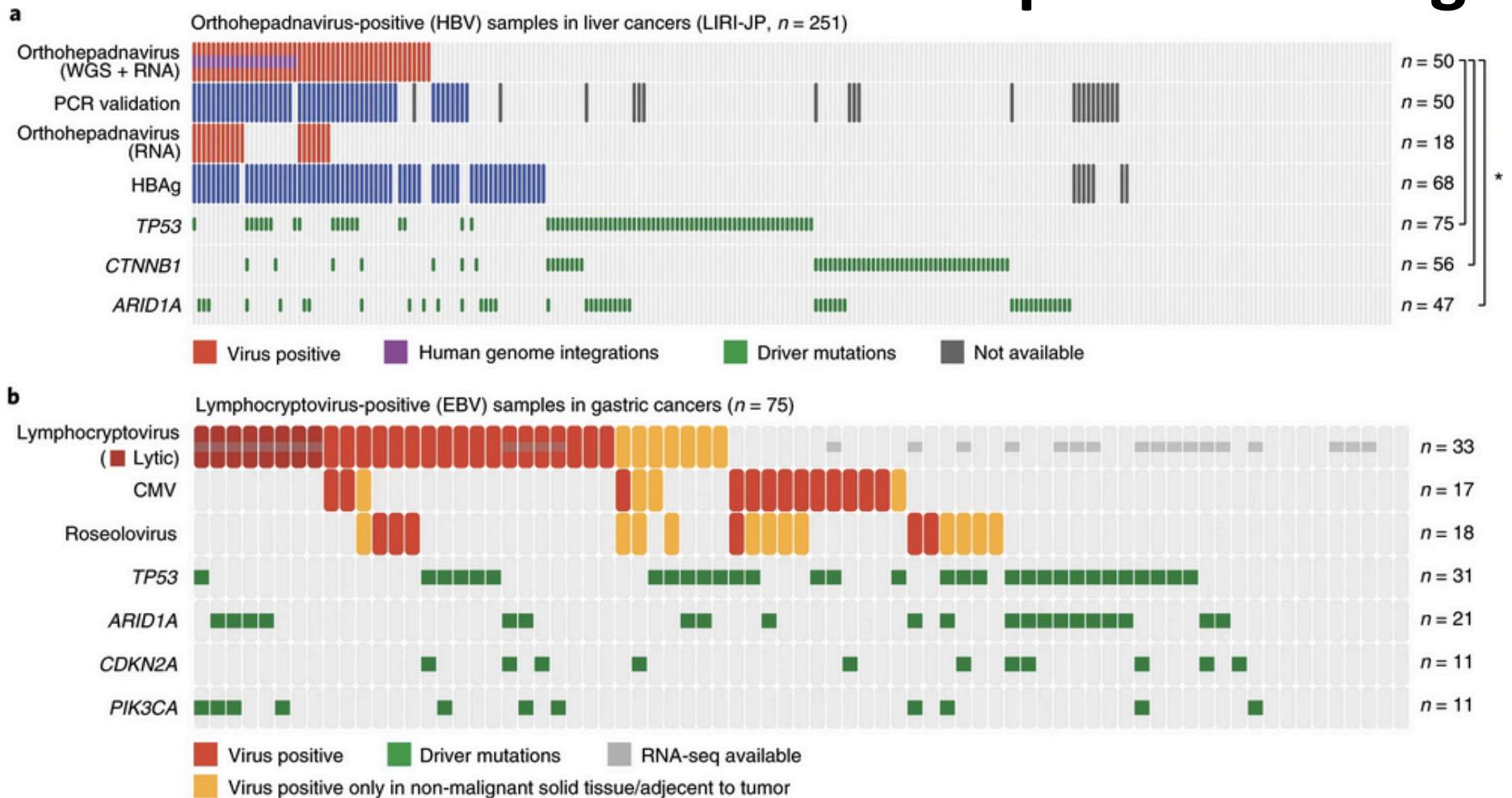
# Viral associations in human cancers

- The World Health Organization estimates that 15.4% of all cancers are attributable to infections and 9.9% are linked to viruses.
  - HPV<sup>4</sup> (associated with 640,000 cases),
  - HBV<sup>5</sup> (420,000 cases),
  - hepatitis C virus (HCV)<sup>6</sup> (170,000 cases)
  - EBV<sup>7</sup> (120,000 cases)

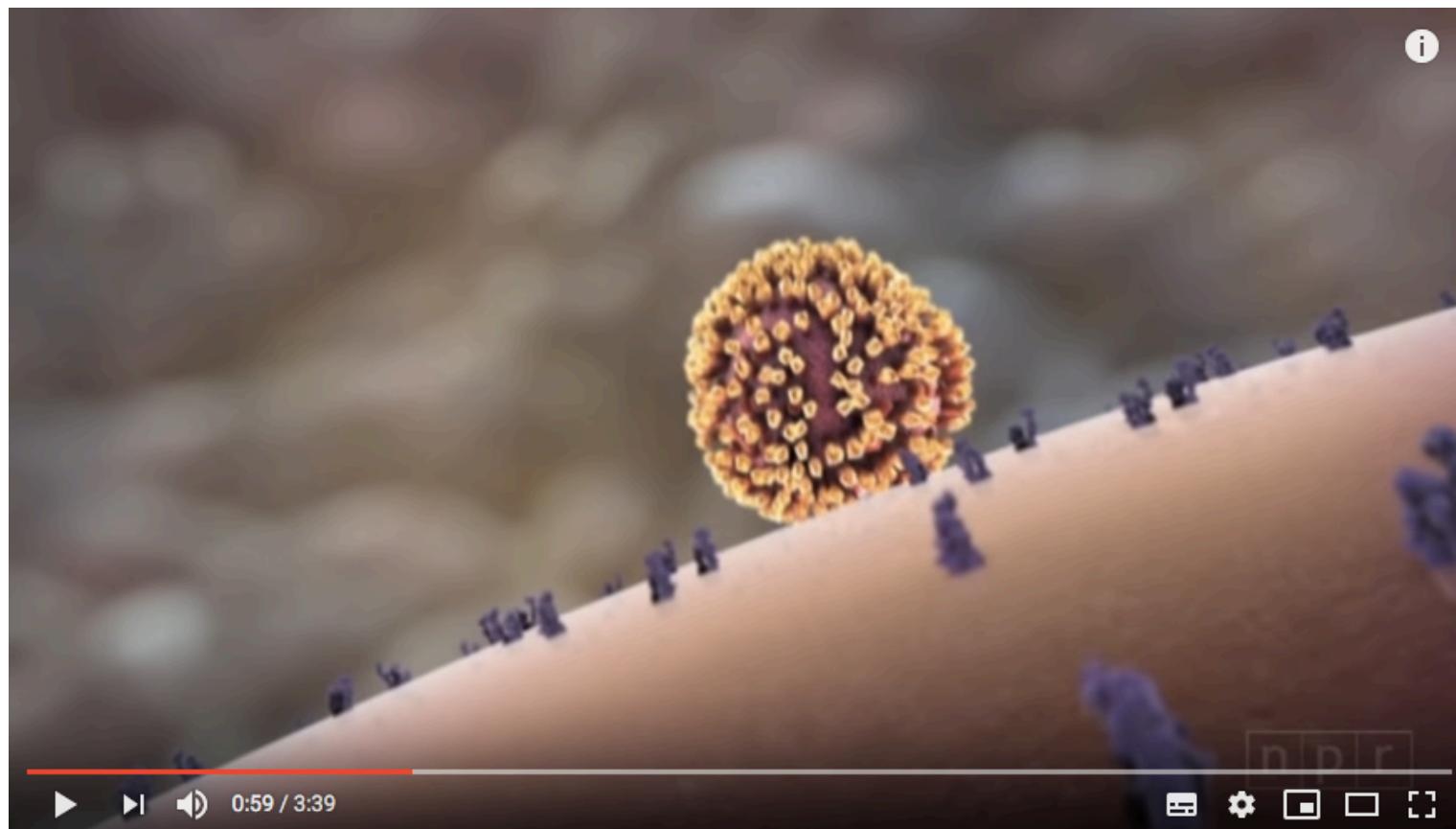
*t*-SNE clustering of the tumor samples based on PMER of their consensus virome profiles



# Virus-specific findings



# How A Virus Invades Your Body



<https://>

# HIV life cycle



<https://www.youtube.com/watch?v=odRyv7V8LAE>

# Immunotherapy

# The Nobel Prize in Physiology or Medicine 2018



© Nobel Media AB. Photo: A.  
Mahmoud

**James P. Allison**  
Prize share: 1/2



© Nobel Media AB. Photo: A.  
Mahmoud

**Tasuku Honjo**  
Prize share: 1/2

The Nobel Prize in  
Physiology or  
Medicine 2018 was  
awarded jointly to  
James P. Allison and  
Tasuku Honjo "for  
their discovery of  
cancer therapy by  
inhibition of negative  
immune regulation."

James P. Allison studied a known protein that functions as a brake on the immune system. He realized the potential of releasing the brake and thereby unleashing our immune cells to attack tumors. He then developed this concept into a brand new approach for treating patients.

In parallel, Tasuku Honjo discovered a protein on immune cells and, after careful exploration of its function, eventually revealed that it also operates as a brake, but with a different mechanism of action. Therapies based on his discovery proved to be strikingly effective in the fight against cancer.

Allison and Honjo showed how different strategies for inhibiting the brakes on the immune system can be used in the treatment of cancer. The seminal discoveries by the two Laureates constitute a landmark in our fight against cancer.



<https://www.youtube.com/watch?v=UbFjiWOBErA>

# Immune Checkpoint Inhibitors



<https://www.youtube.com/watch?v=GIUu239FWMg>