

June, 2023

Realidades y Esperanzas

una reflexión muy personal sobre el cáncer...

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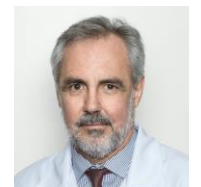
Disclosures

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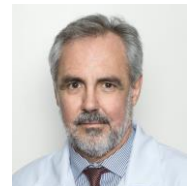
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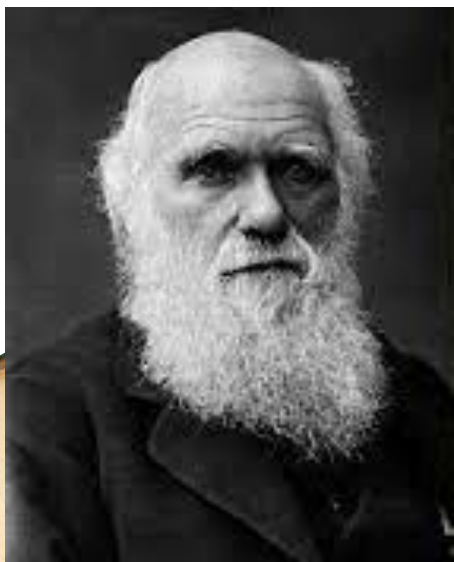


The hominin wall at the Natural History Museum of Utah in Salt Lake City. (Image credit: Copyright NHMU/Credit: Mark Johnston)



**“Life is a self-sustaining chemical system
capable of Darwinian evolution”**

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ON
THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,
OR THE
PRESERVATION OF FAVOURED RACES IN THE STRUGGLE
FOR LIFE.

By CHARLES DARWIN, M.A.,
FELLOW OF THE ROYAL, ANATOMICAL, LINNEAN, ETC., SOCIETIES;
AUTHOR OF 'JOURNAL OF RESEARCHES DURING H. M. S. BEAGLE'S VOYAGE
AROUND THE WORLD.'

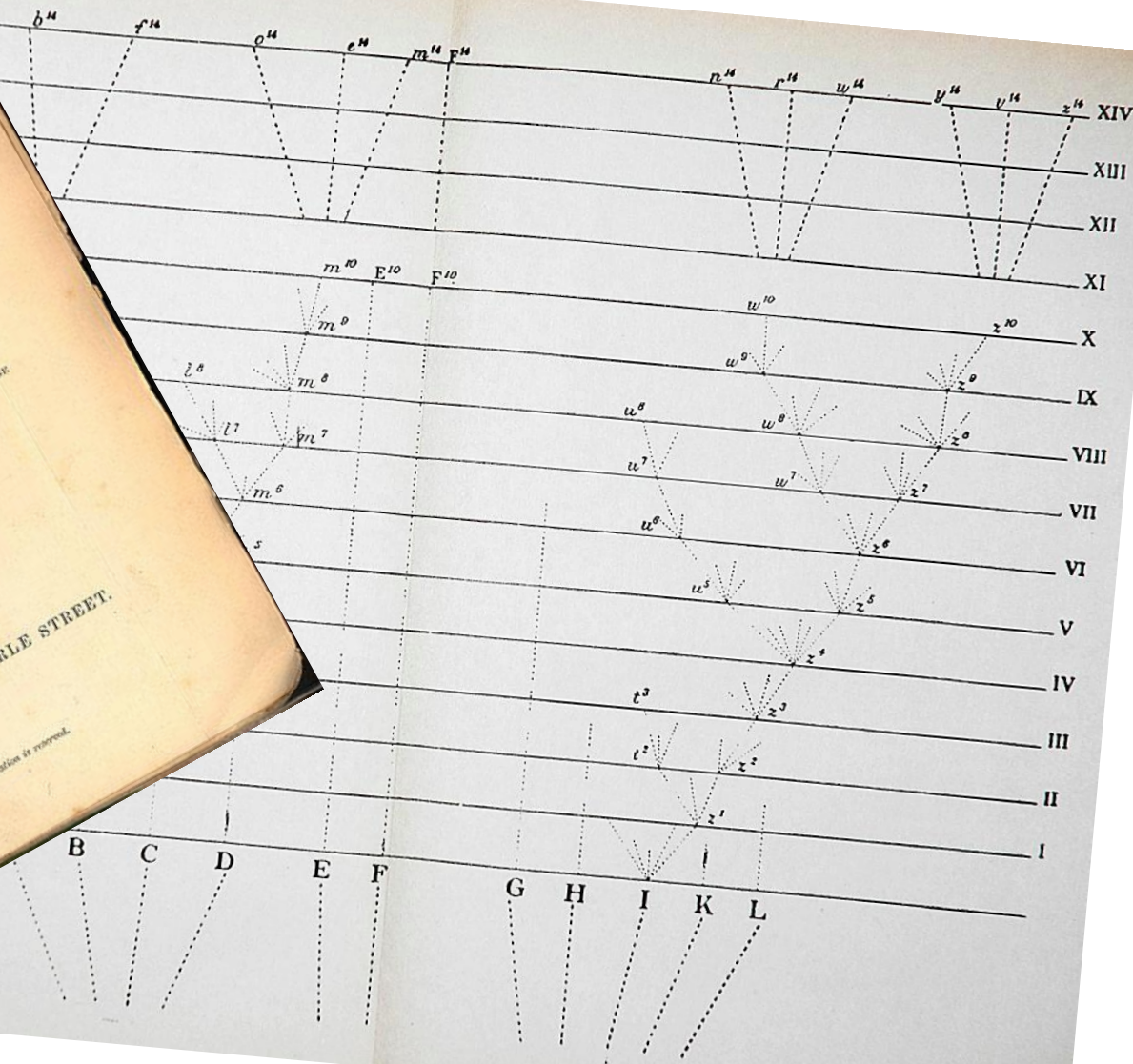
LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1859.

The right of Translation is reserved.

"But with regard to the material world, as far as this—we can perceive that events are brought about by insulated interpositions of Divine power, exerted in each particular case, but by the establishment of general laws."
W. WHEWELL: *Bridgewater Treatise*.

"To conclude, therefore, let no man out of a weak conceit of sobriety, or an ill-applied moderation, think or maintain, that a man can search too far or be too well studied in the book of God's word, or in the book of God's works; divinity or philosophy; but rather let men endeavour an endless progress or proficience in both."
Bacon: *Advancement of Learning*.

Dover, Broxley, Kent,
October 1st, 1859.



"Darwin's tree of life," por Charles Darwin. Fotografia por A. Kouprianov, domínio público.

•WINNER OF THE PULITZER PRIZE•

THE
EMPEROR
OF ALL
MALADIES



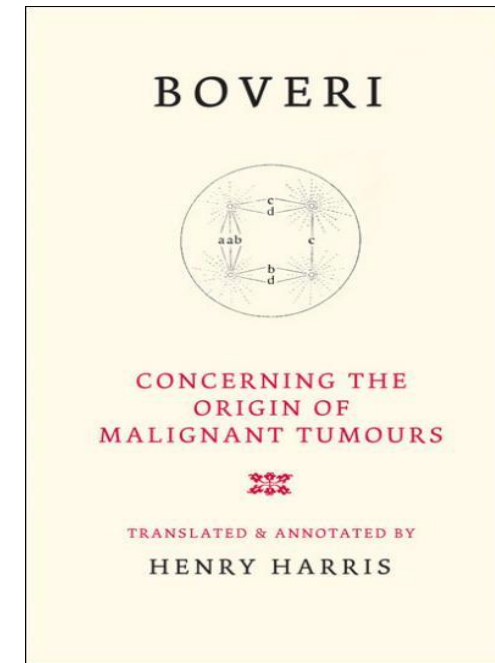
READ BY
FRED SANDERS

A BIOGRAPHY OF CANCER

SIDDHARTHA
MUKHERJEE

"A compulsively readable, surprisingly uplifting, and vivid tale. Thrilling."

—O, THE OPRAH MAGAZINE



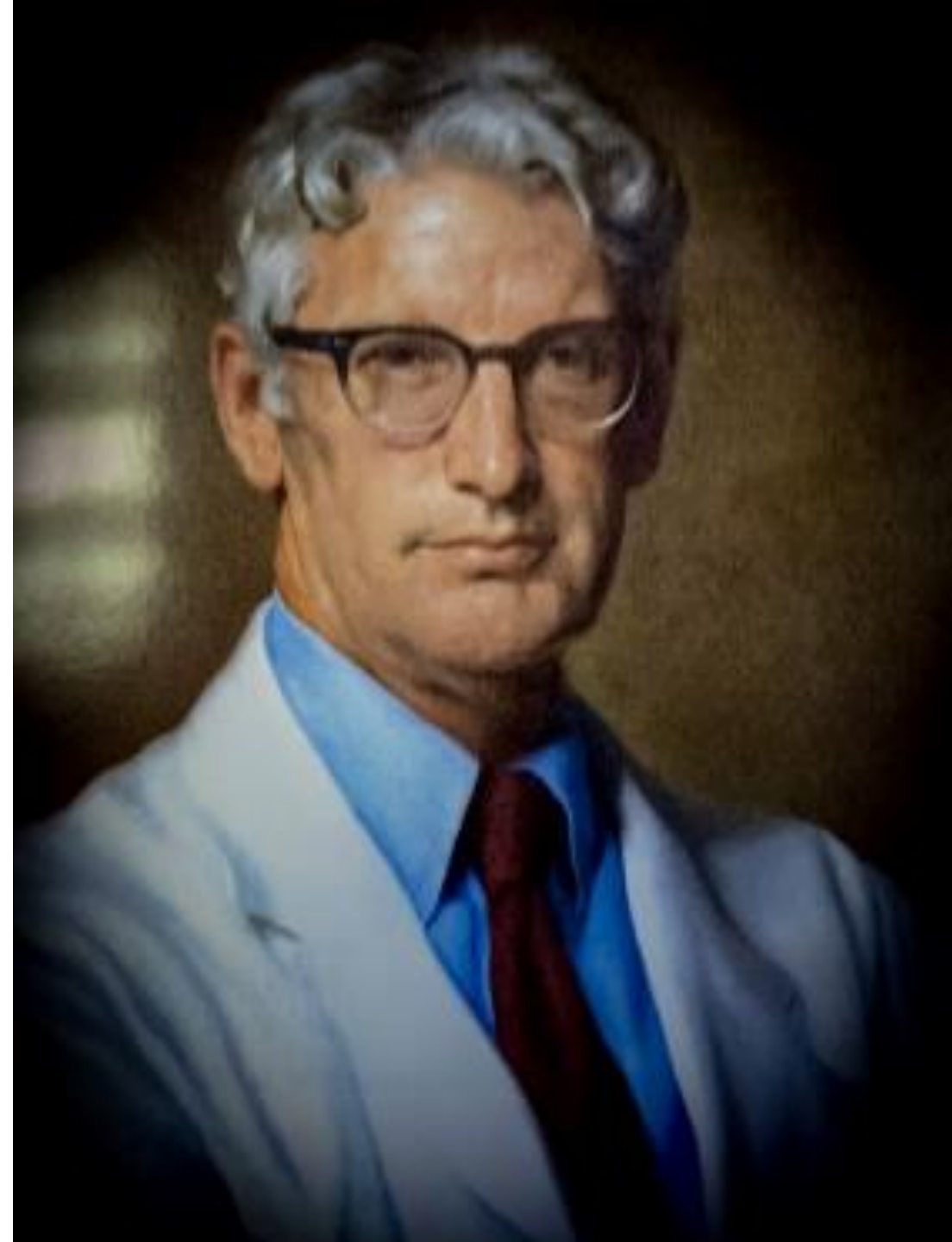
- ***Cancers arise from single cells.***
- ***Loss of key cellular attributes***, (tumor suppressor genes), are a key driver event in the development of cancer
- ***Inheritance*** could play a role in cancer susceptibility.
- ***Chromosomal (genomic) instability*** as key hallmark of cancer
- Genetic information could be contained in ***distinct packages*** (genes) that are linearly arranged along chromosomes

(1862-1915)

The Clonal Evolution of Tumor Cell Populations

Acquired **genetic lability** permits stepwise selection of variant sublines and underlies tumor progression.

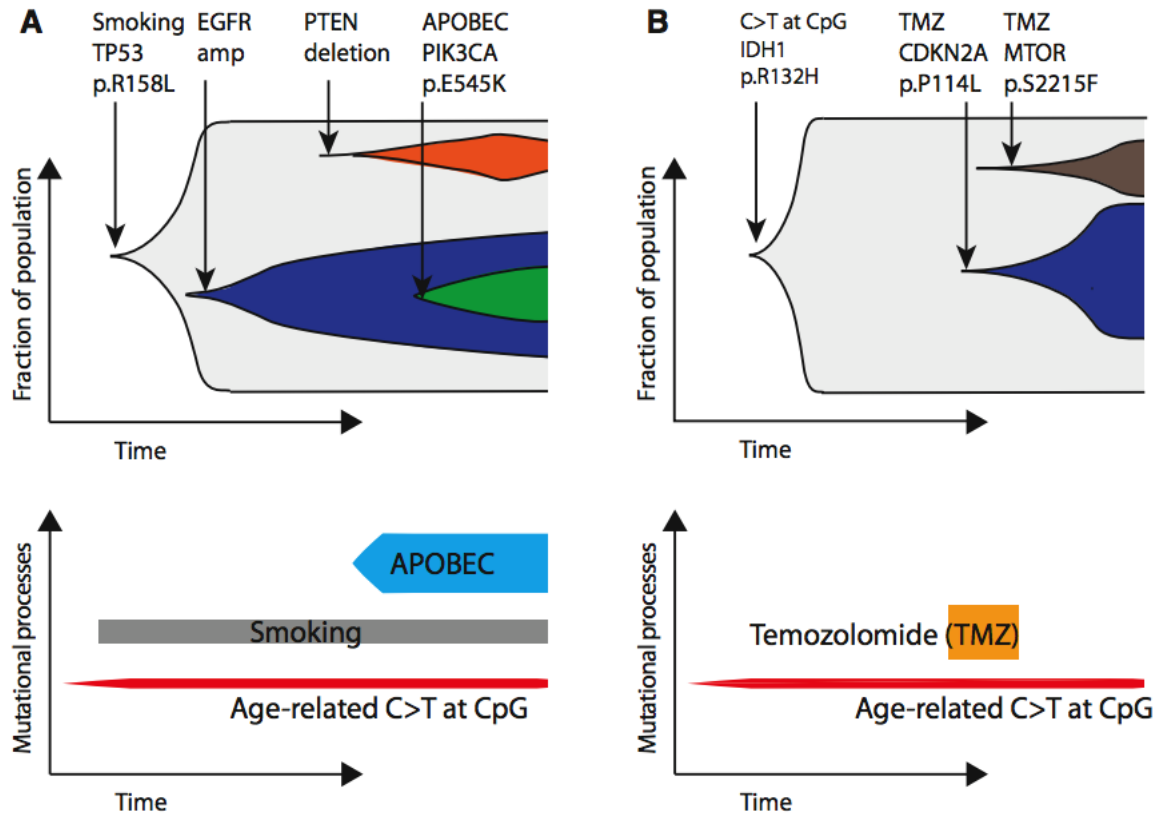
(P Nowell)



**From a biologic and
evolutionary point of
view, cancer is an almost
unavoidable or inevitable
outcome (event)**

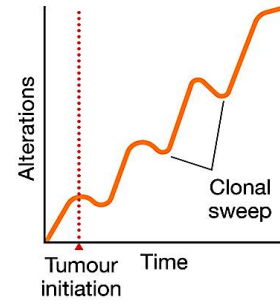
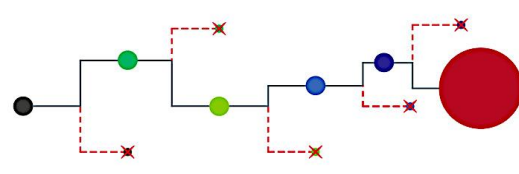
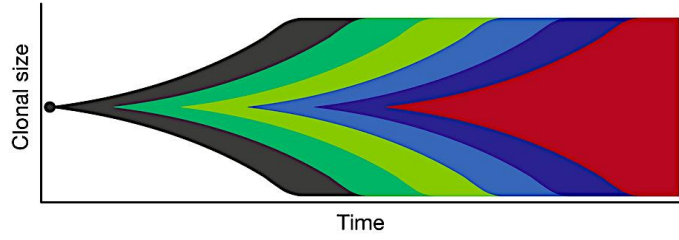
Cancer as a reactive process, is nothing more than an attempt to survive and therefore reach immortality...

Endogenous and Exogenous Mutational Processes are key in the Evolutionary Trajectory of a Tumor

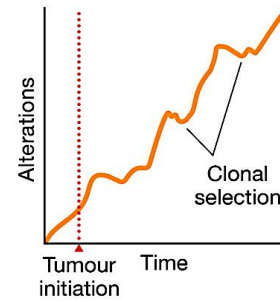
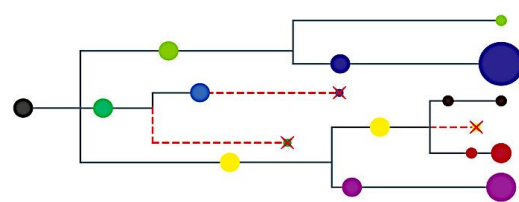
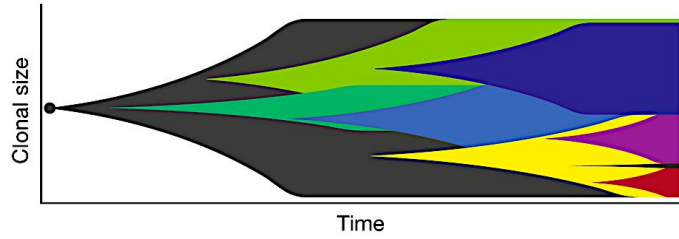


- (A) An age-related mutational process operates throughout the evolution of a lung tumor. A smoking-induced C > A mutation in TP53 (p.R158L) leads to the outgrowth of a major tumor clone. Later in tumor evolution, APOBEC-mediated mutagenesis results in a mutation to PIK3CA (p.E545K), which leads to a subclonal expansion.
- (B) The evolution a glioblastoma tumor that has undergone treatment with Temozolomide (TMZ). Notably, TMZ leads to mutations in CDKN2A and RB1 in separate subclones, both of which lead to subclonal expansions.

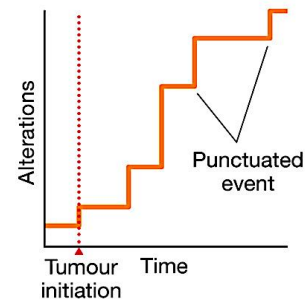
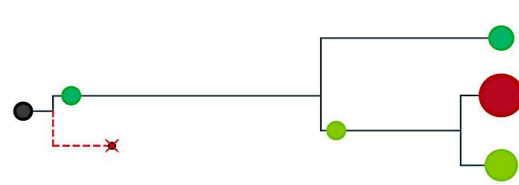
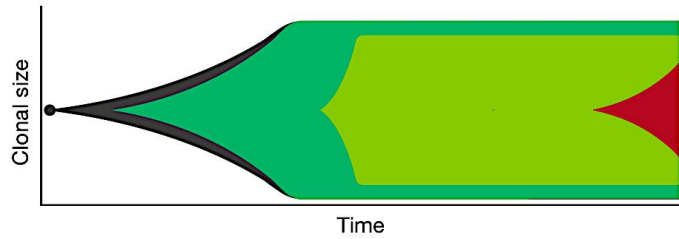
A Linear evolution



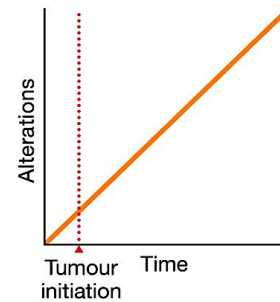
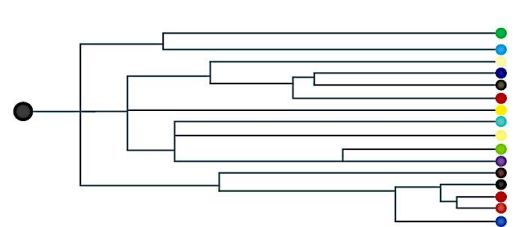
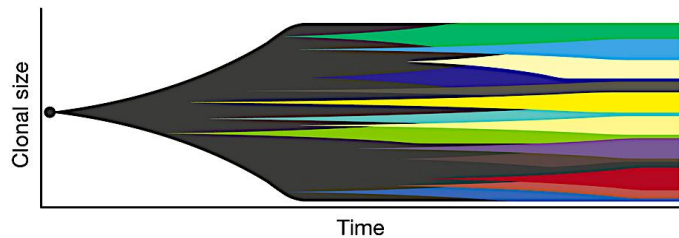
B Branched evolution



C Macroevolution

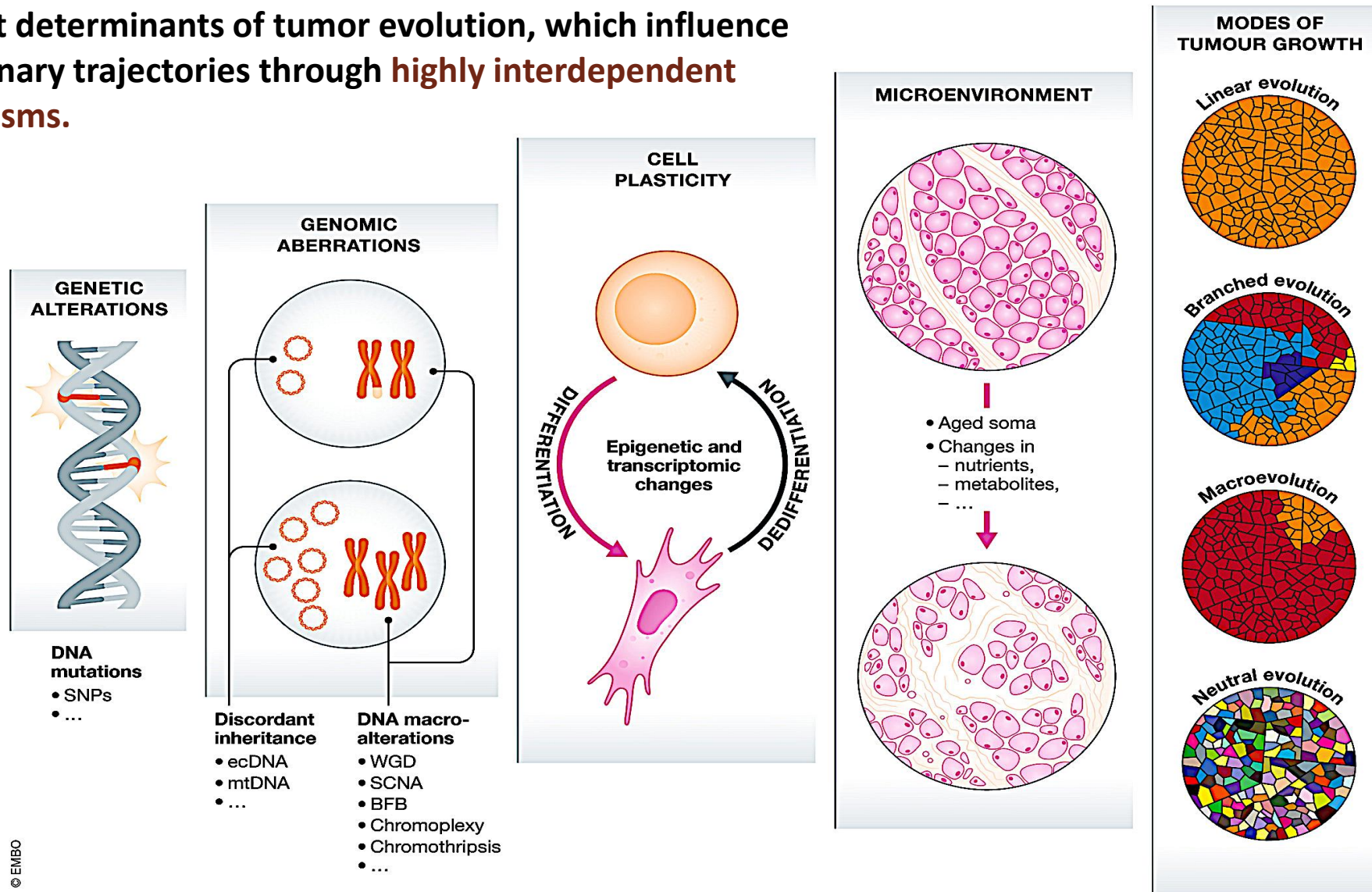


D Neutral evolution



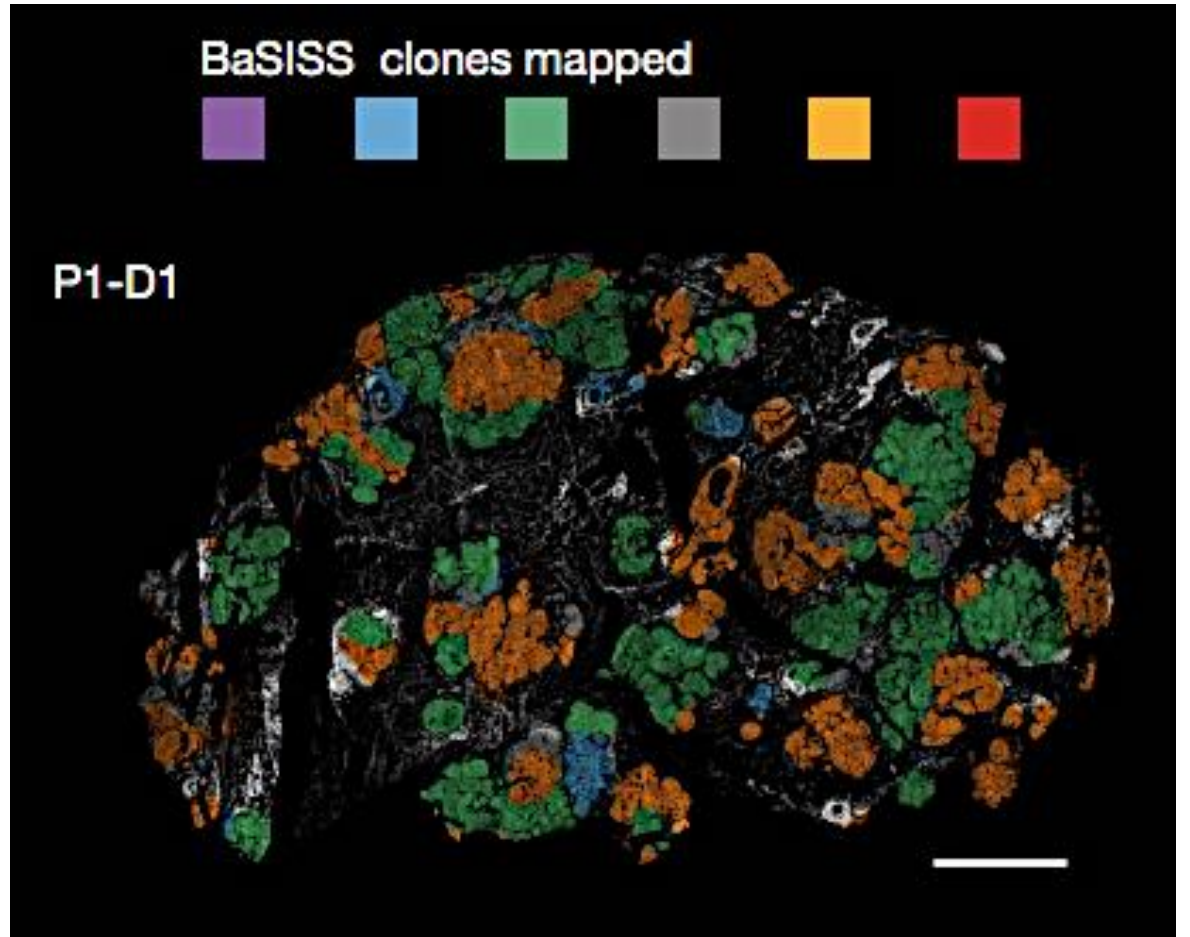
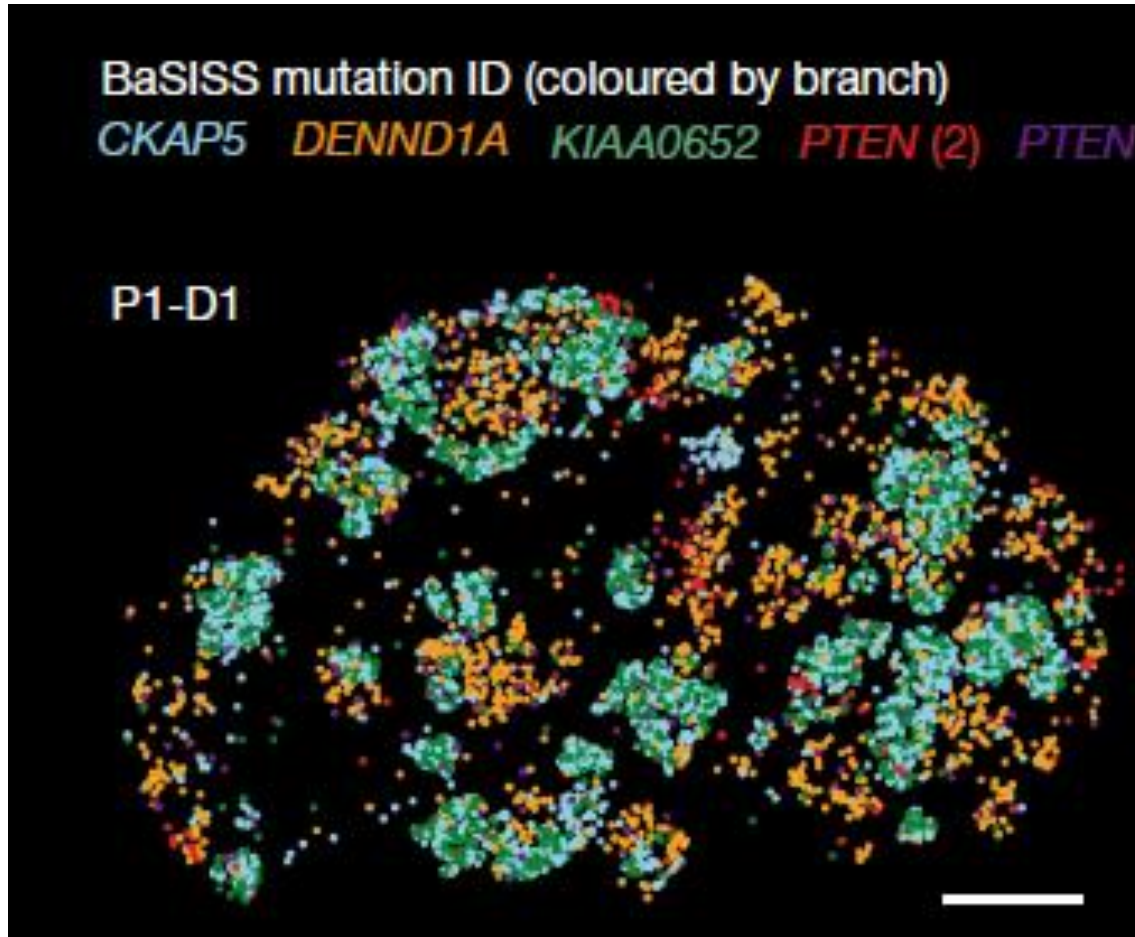
Cancer: Speeding up Darwin's evolution

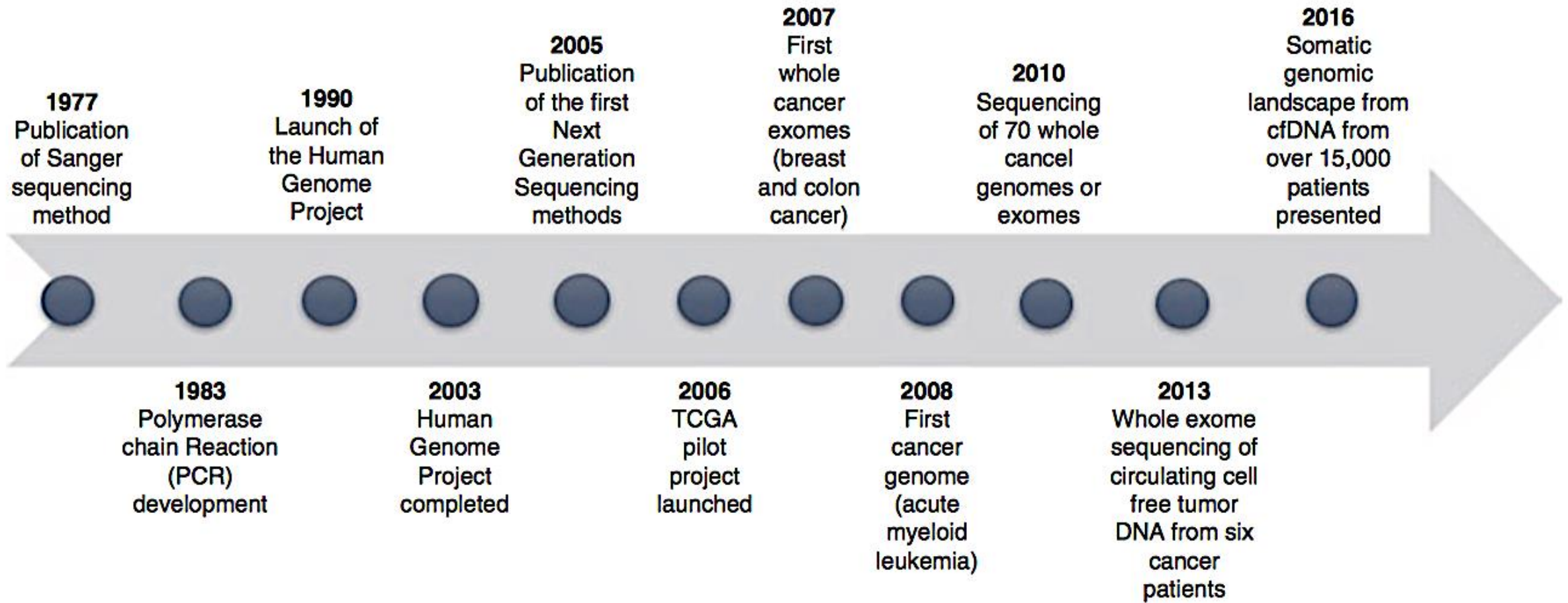
Different determinants of tumor evolution, which influence evolutionary trajectories through **highly interdependent mechanisms**.



© EMBO

Spatial genomics maps the structure, nature and evolution of cancer clones

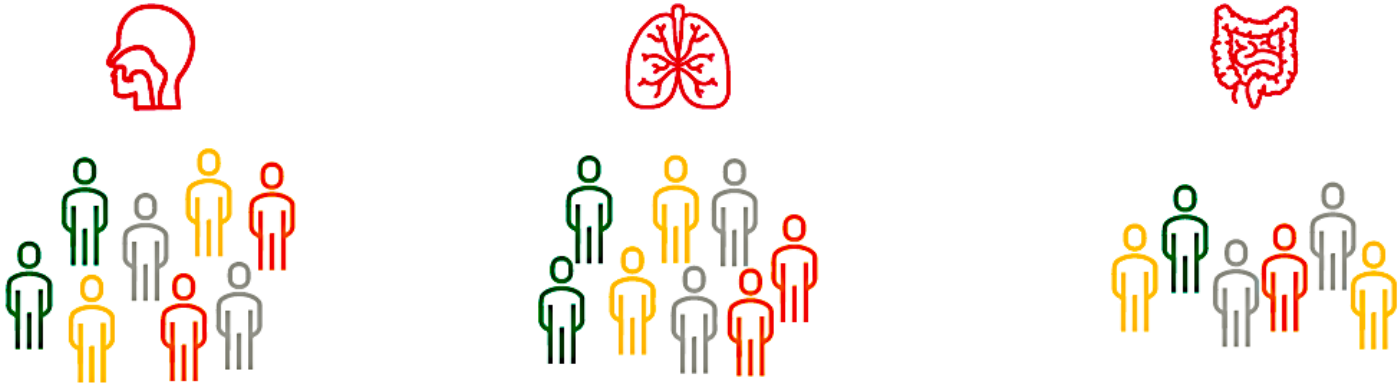




Impact of Personalized Approaches in Clinical Practice

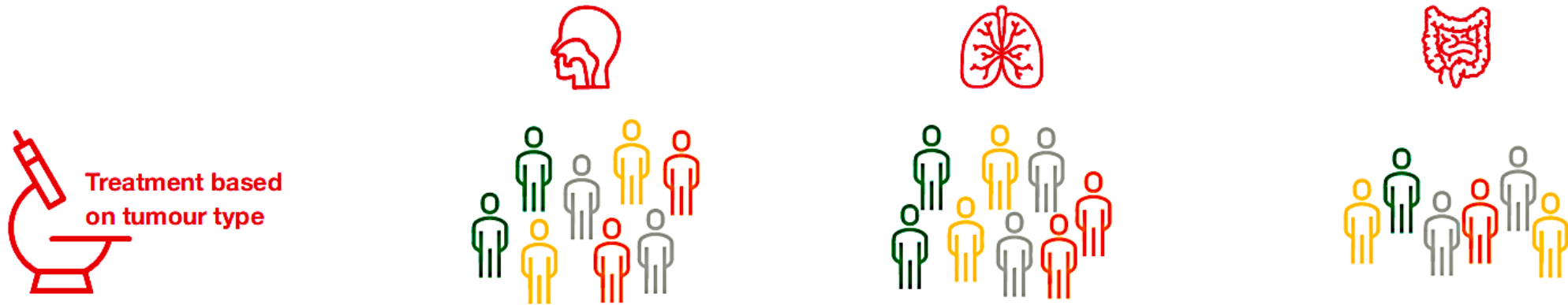


Impact of Personalized Approaches in Clinical Practice



MOLECULAR PROFILING / DIAGNOSIS

Impact of Personalized Approaches in Clinical Practice

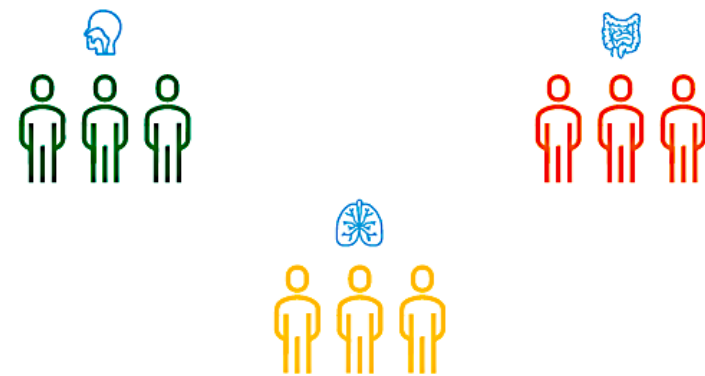


MOLECULAR PROFILING / DIAGNOSIS

Tumour-agnostic treatment based on a biomarker

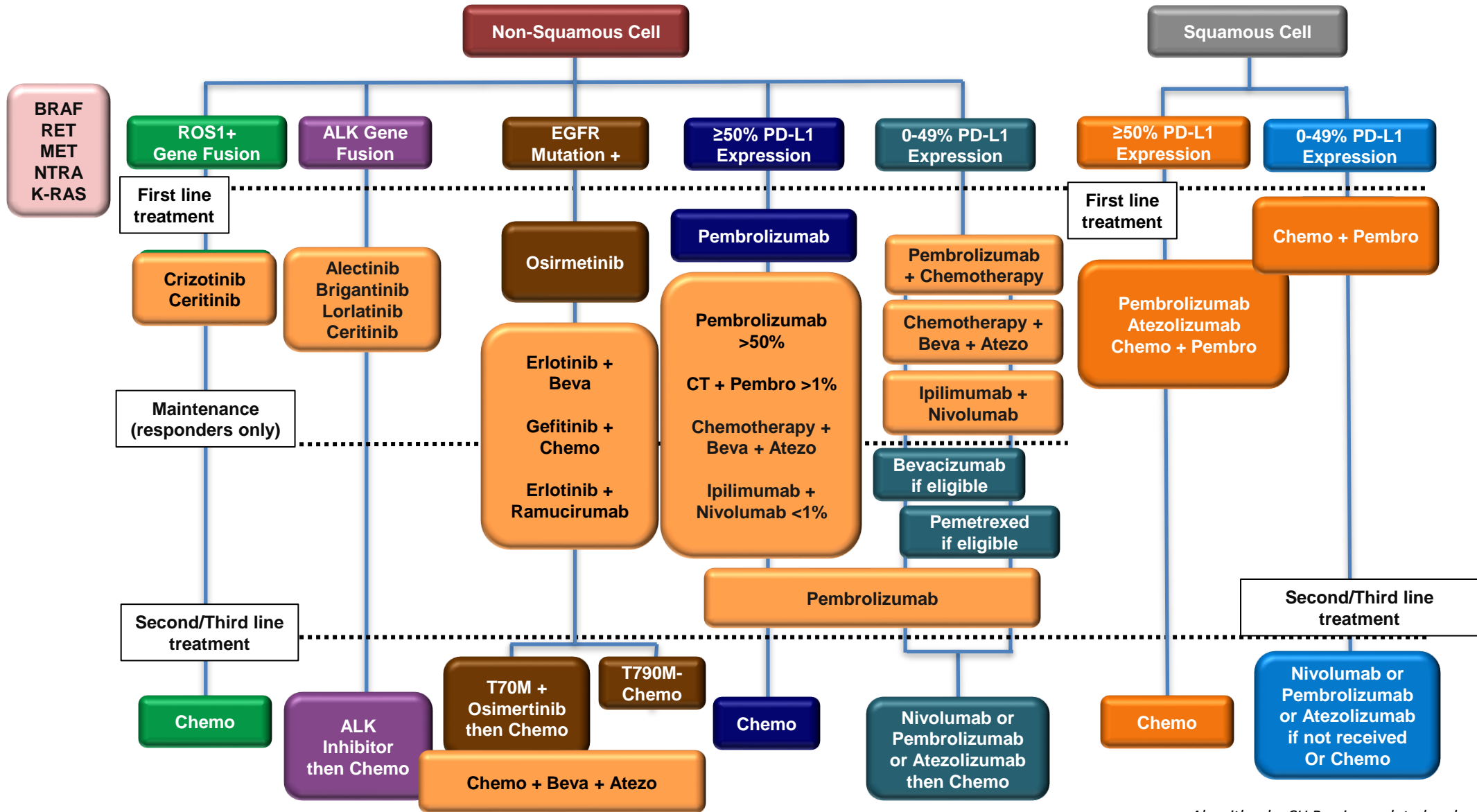


Targeted treatment driven by a biomarker-defined population

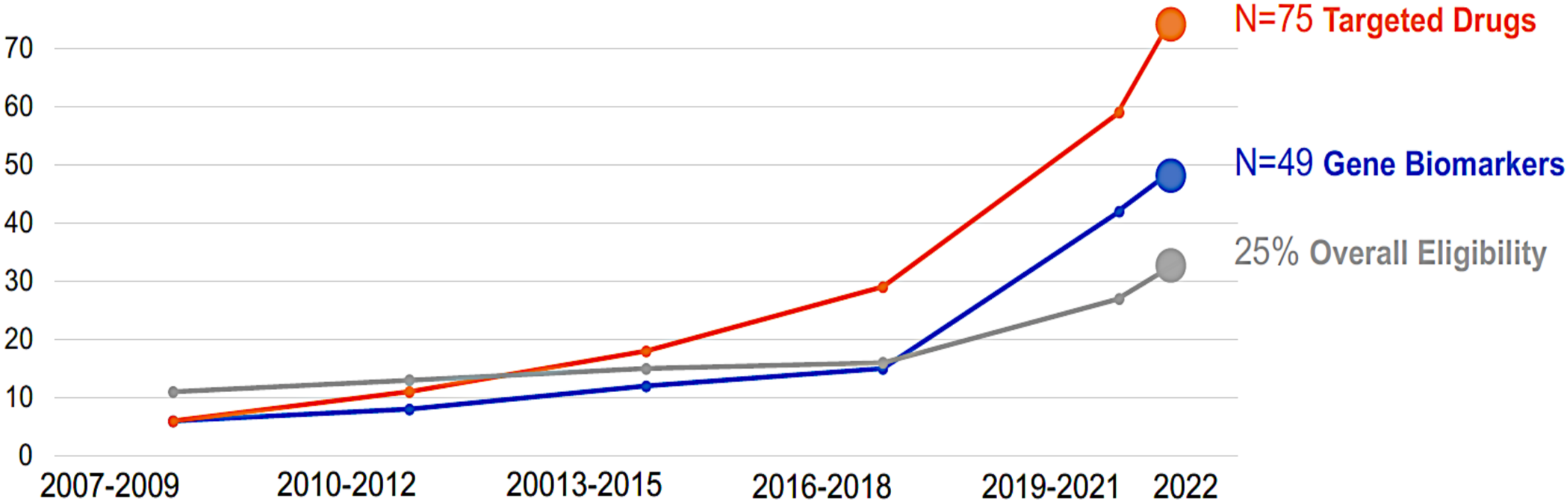


* This algorithm is responsibility of the author, is presented for didactic purposes only and may not necessarily be in accordance to approved therapies in certain countries. Please refer to your applicable approved indications.

Proposed Standard of Care Treatment Algorithm for Patients with Advanced NSCLC – 2022*

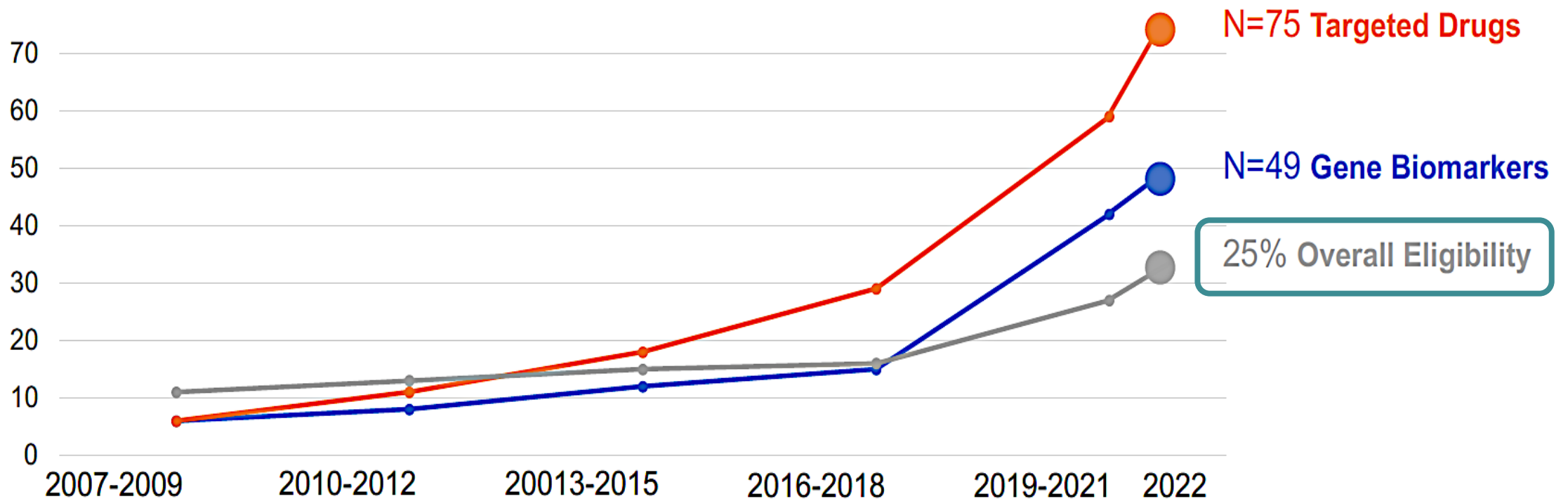


Genomics and Cancer Therapy: Hope or Hype!

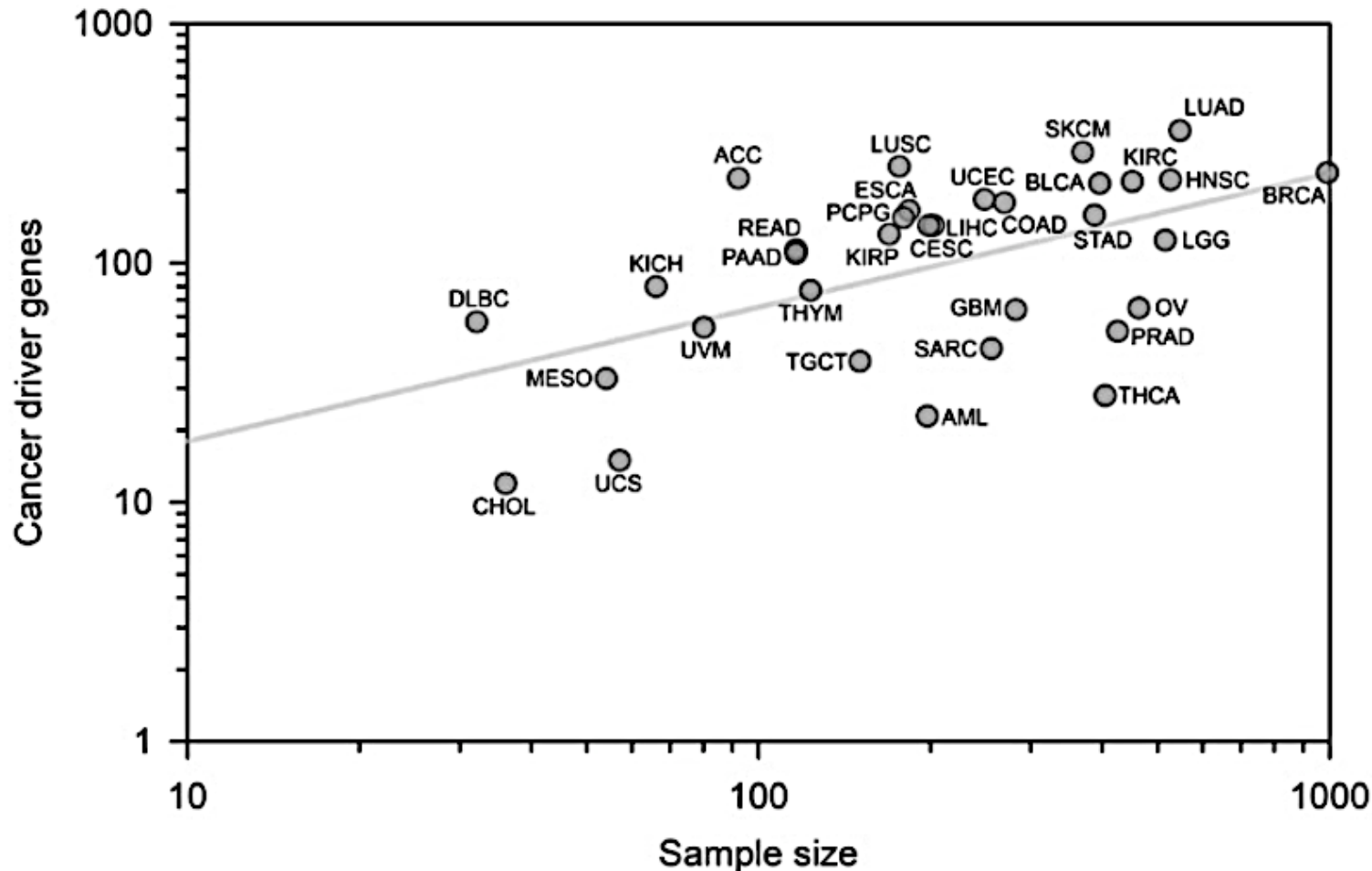


Haslam et al, Ann Oncol, 2021
Diestmann R, et al, Ann Oncol, 2021

Genomics and Cancer Therapy: Hope or Hype!

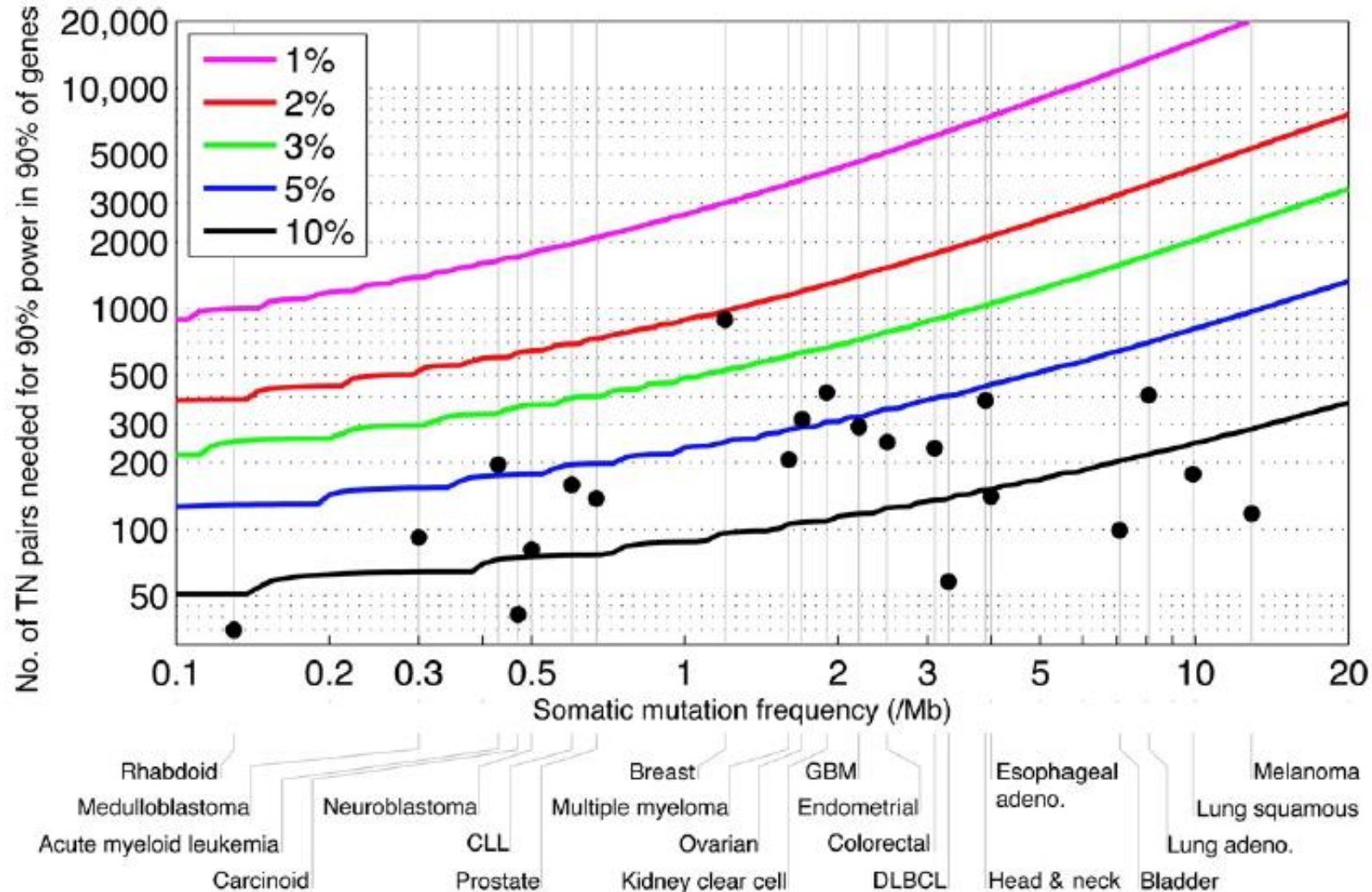


Further increase in sample size does not increase gene identification



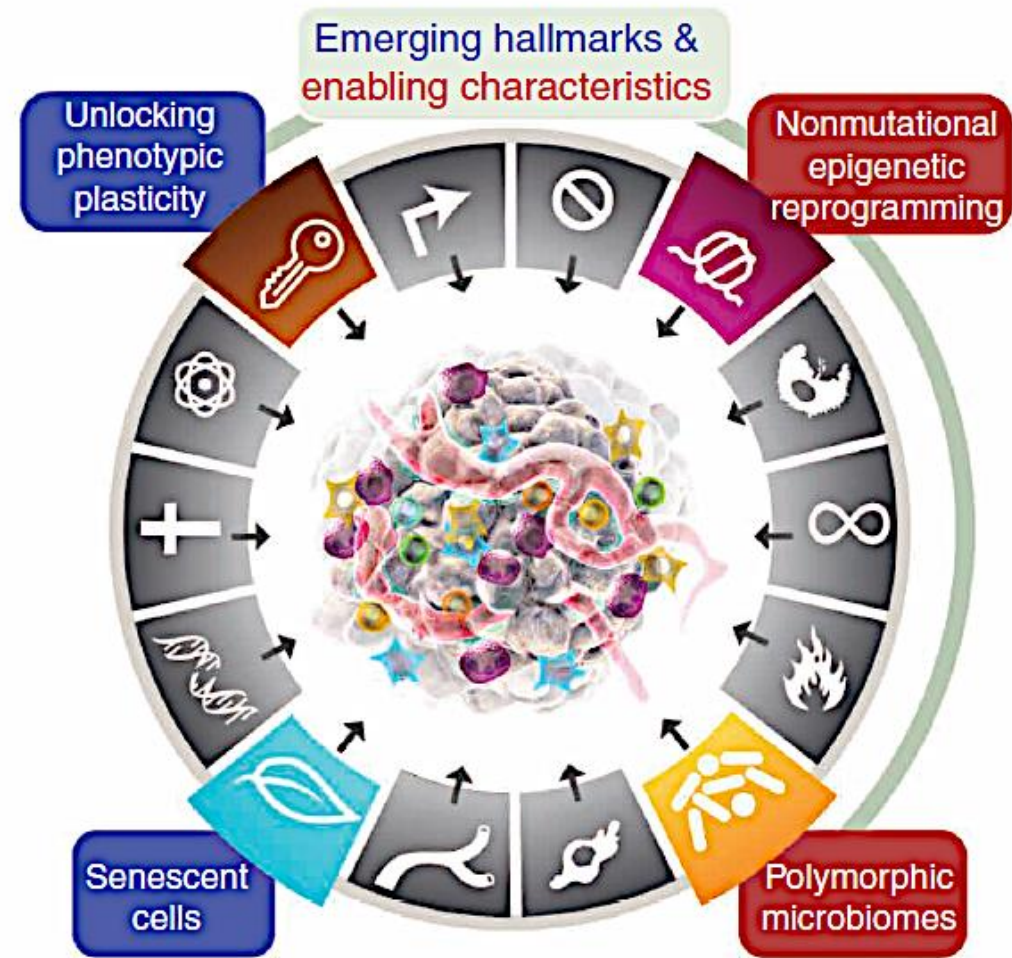
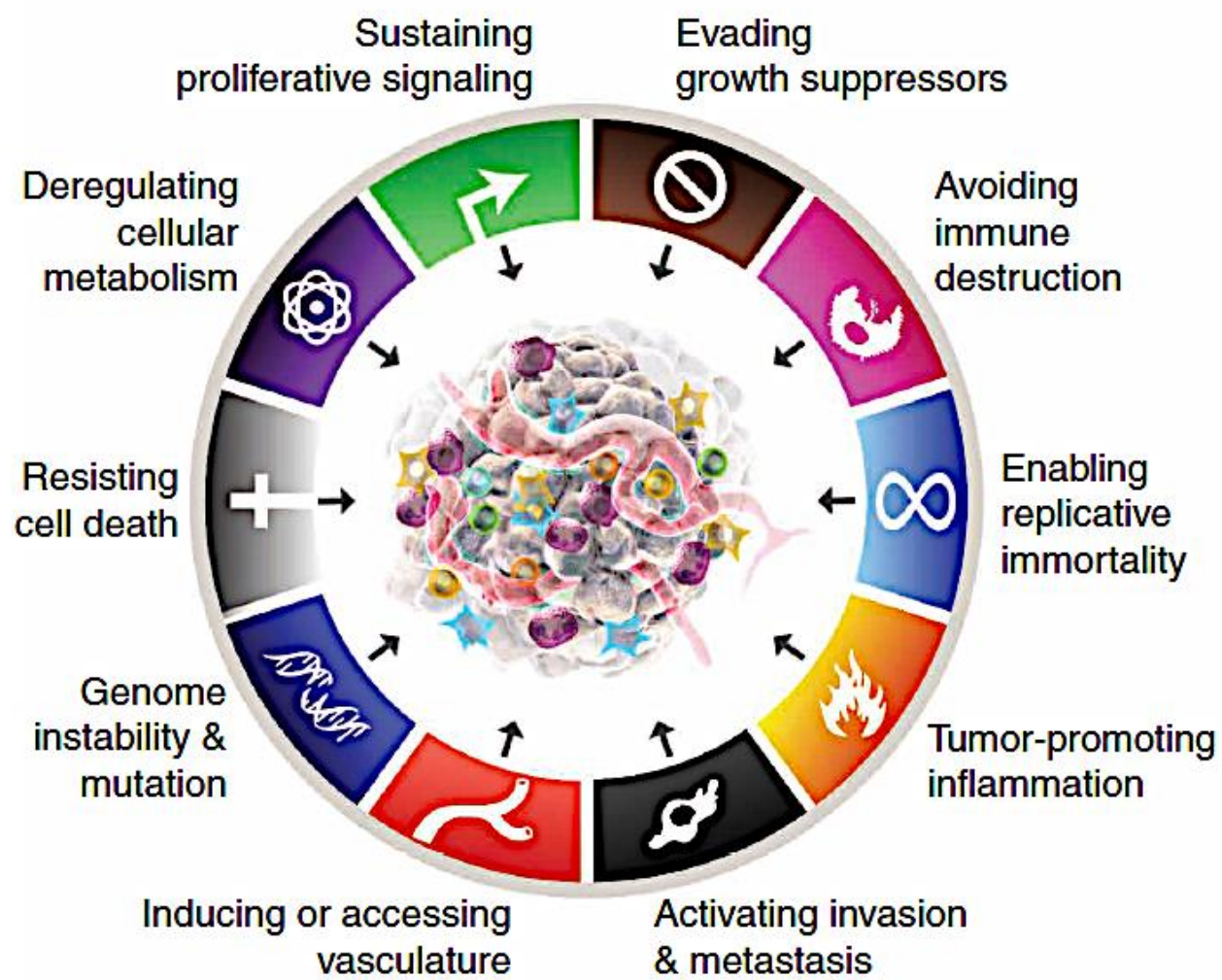
- Positive correlation between sample size and identified driver gene mutations across 33 cancers
- **Sequencing as many specimens as possible for all cancer types is becoming inefficient.**

Near saturation may achieved with 600-5000 samples/tumor

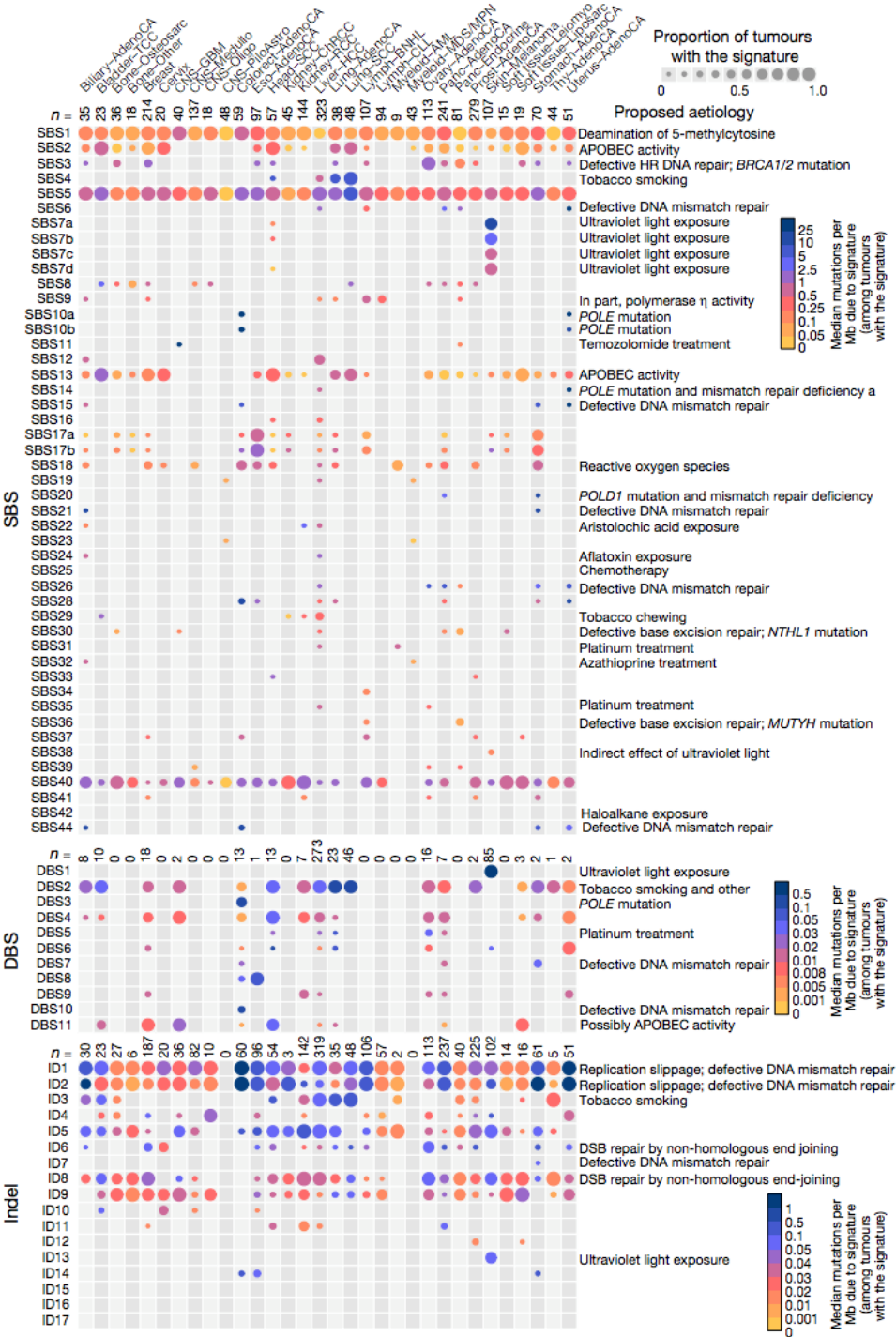


**Genes (sequencing)
do not hold all the answers...**

There is (much) more to cancer than gene abnormalities

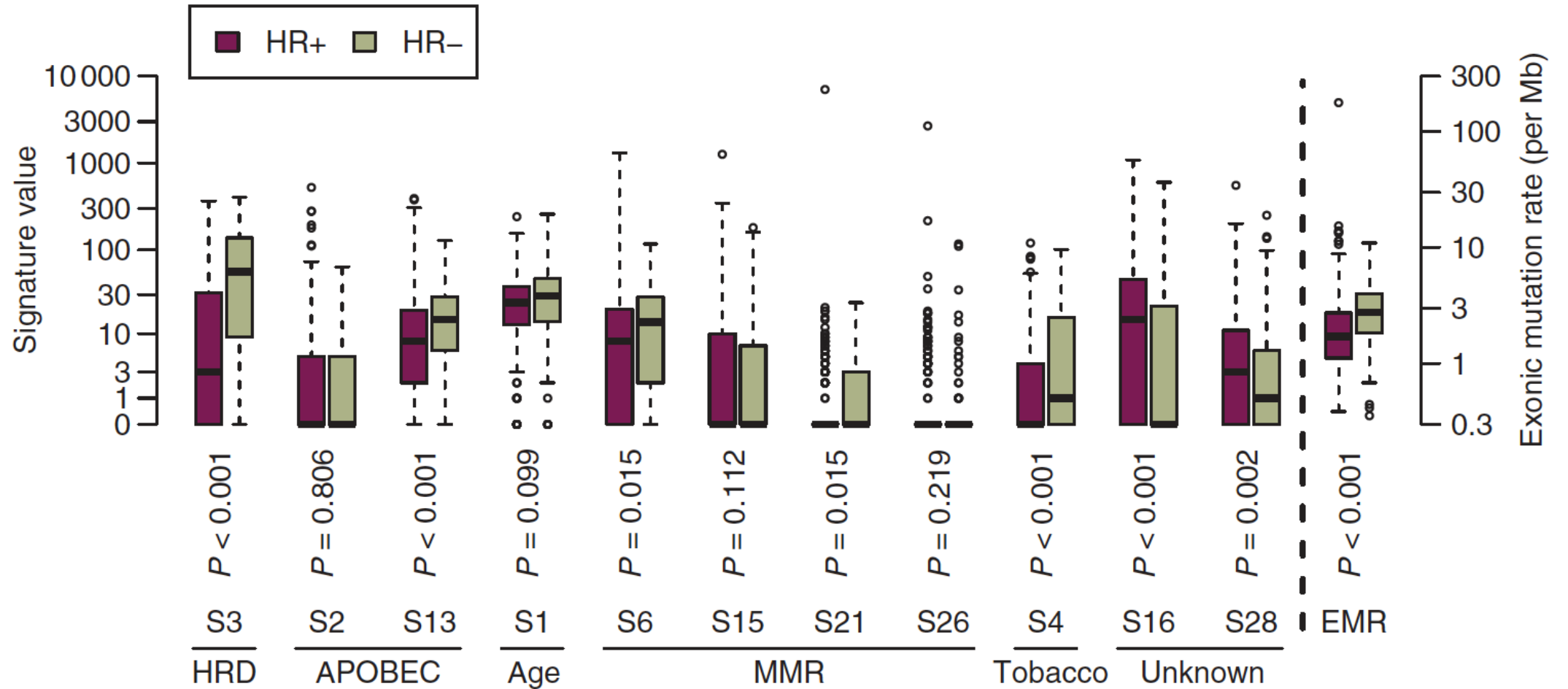


Genomic Signatures

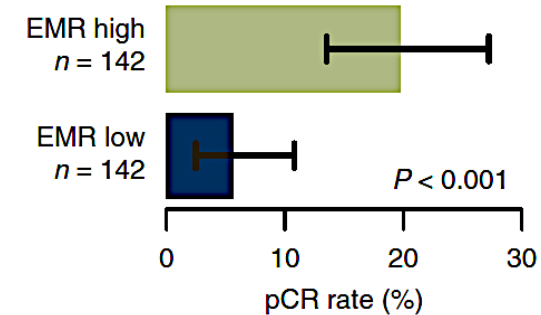
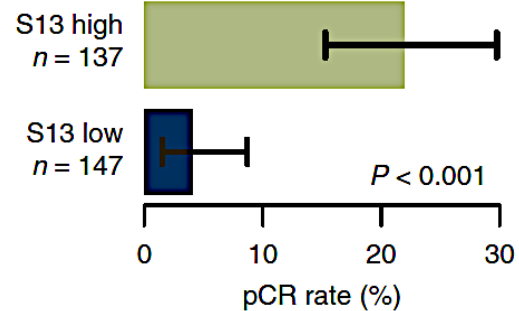
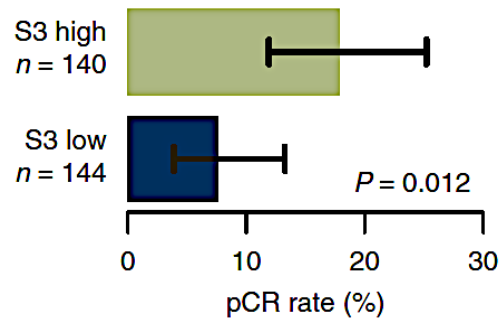
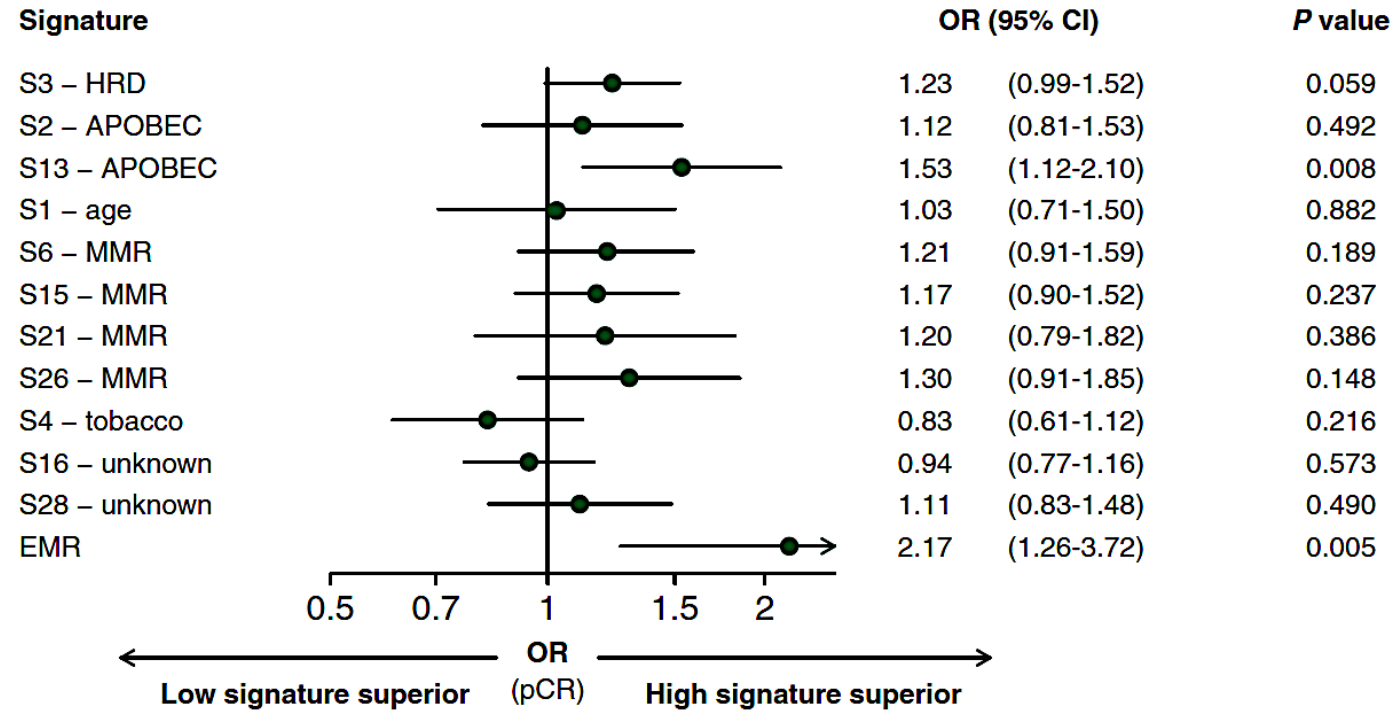


- Exogenous or endogenous exposures and defective DNA repair/maintenance generate **mutational signatures** including base substitutions, small insertions and deletions, rearrangements and chromosome copy-number changes. (i.e., multiple mutational processes, each generating a characteristic mutational signature)
- Identified: 49 single-base-substitution, 11 doublet-base-substitution, 4 clustered-base-substitution and 17 small insertion-and-deletion signatures.
- Some signatures are associated to unknown causes.

Mutational Signatures in HR+ and HR- Breast Cancers

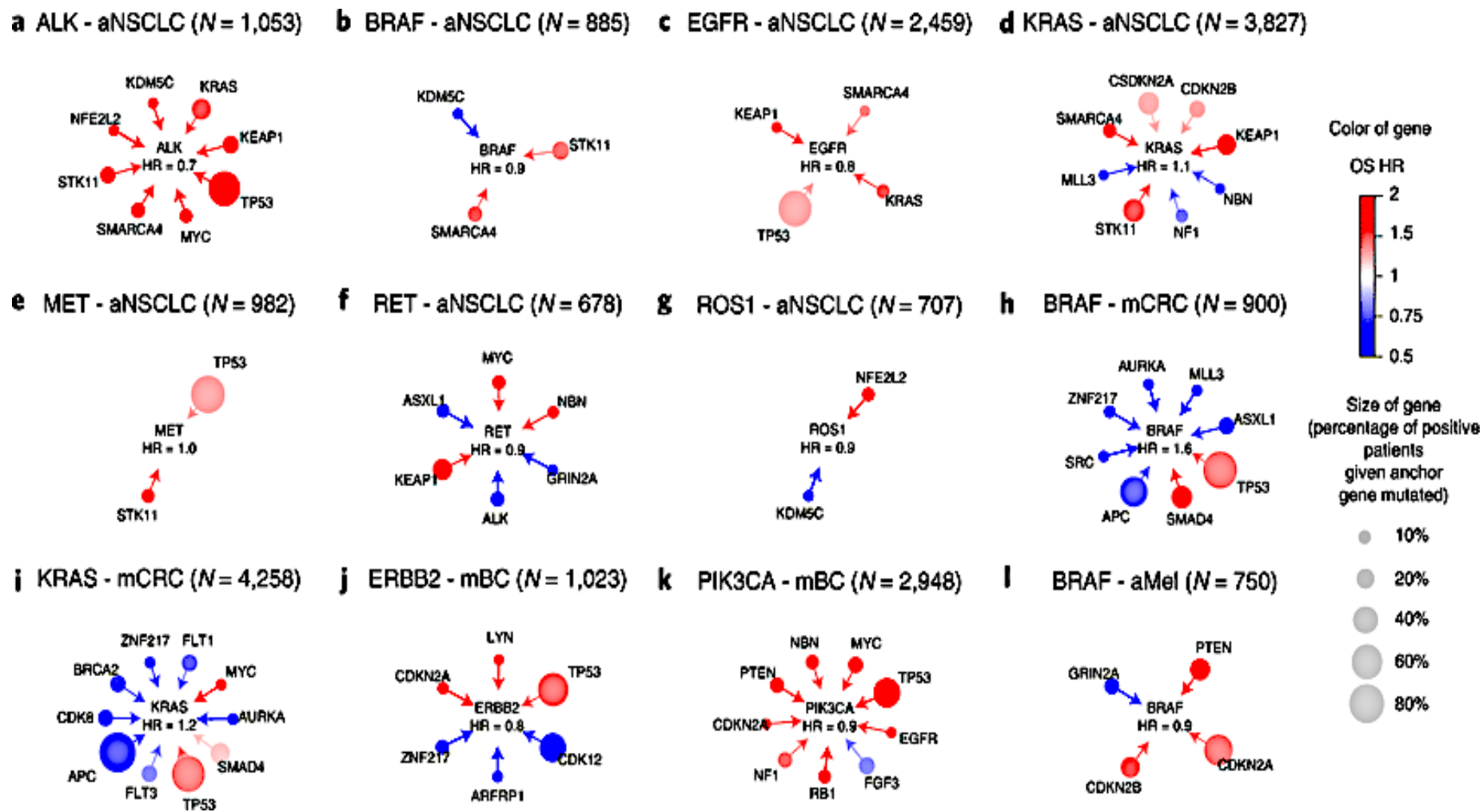


Response to neoadjuvant chemotherapy in HR+ tumors: multivariable analysis and differences in pCR rate



Mutations, Co-Mutations and Modifiers

Computational Analysis of RWD (N=40,903)



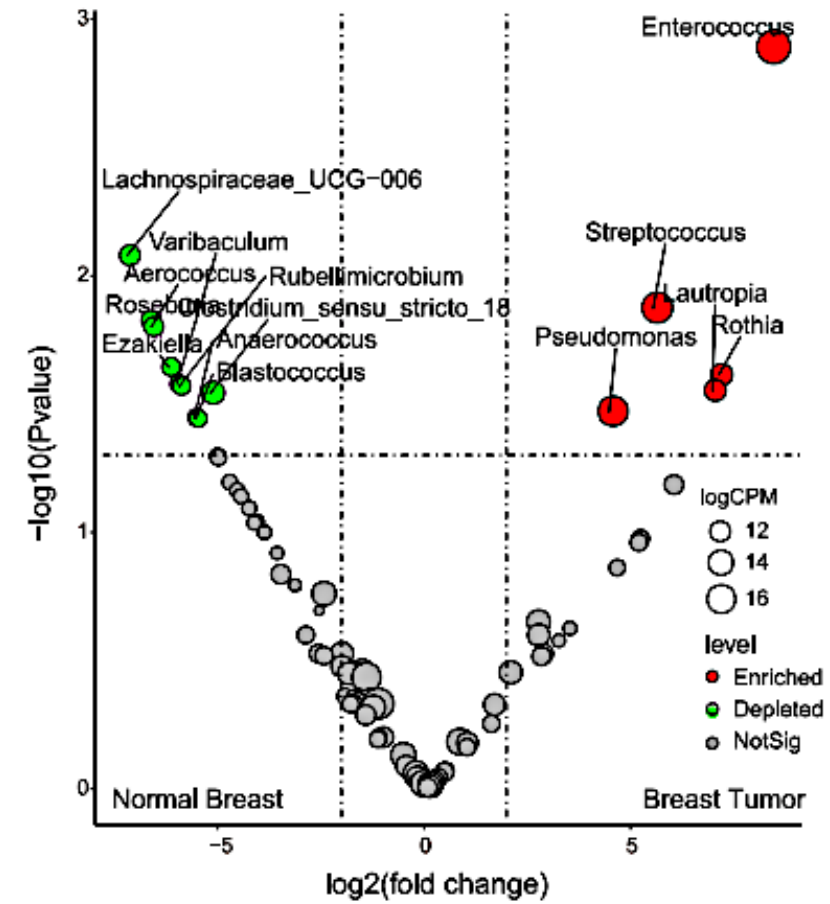
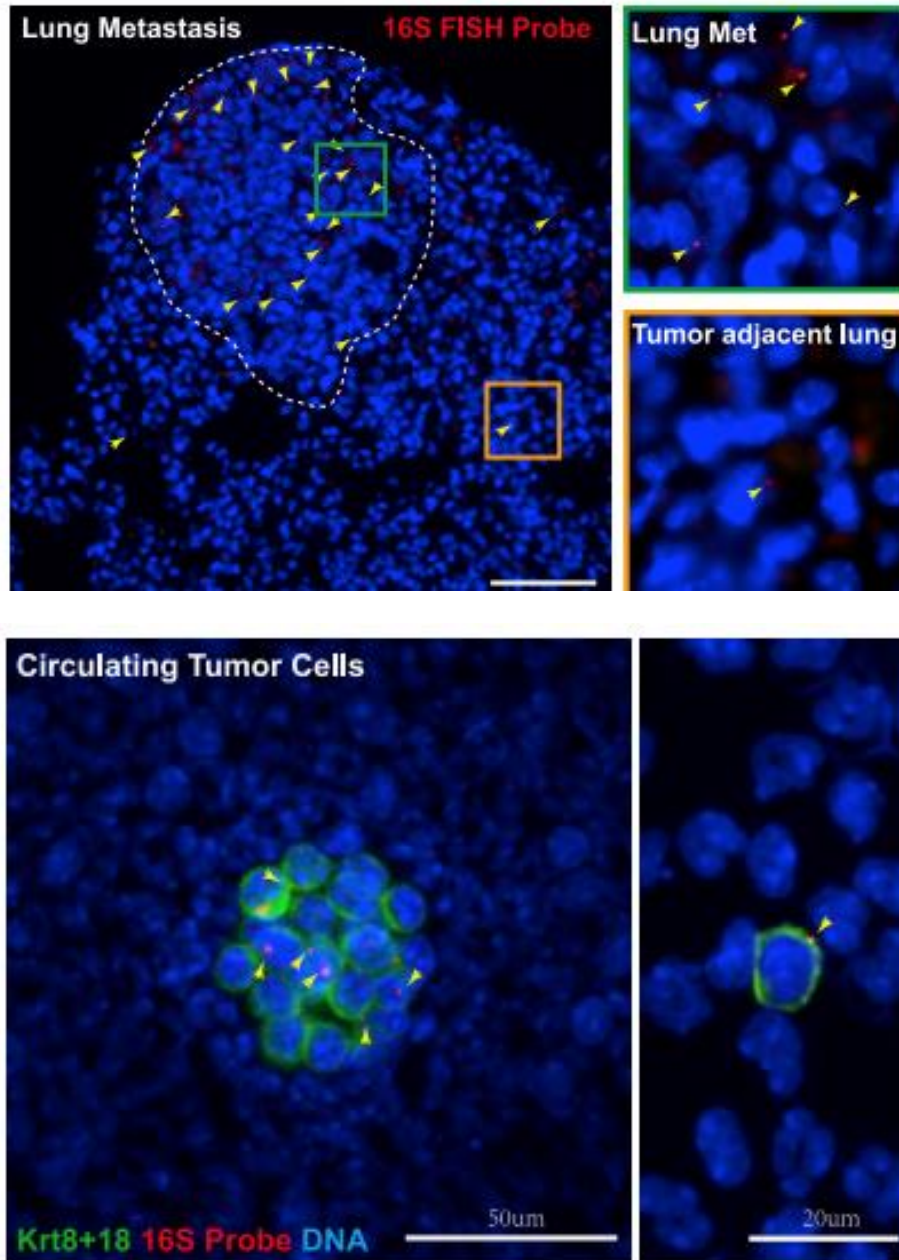
Anchor genes are selected to be genes with available targeted therapies and are shown in the middle of each panel together with their prognostic HRs for OS.

Modifiers are genes with significant anchor–modifier interactions (two-sided Wald test P value <0.05 and FDR <0.05).

The size of a modifier gene’s circle indicates what fraction of patients with the anchor gene mutated also have mutation in the modifier gene.

The modifier’s color indicates its positive (blue for HR <1) or negative (red for HR >1) impact on the survival of patients who have the anchor gene mutation.

Tumor-resident intracellular microbiota promotes metastatic colonization in breast cancer



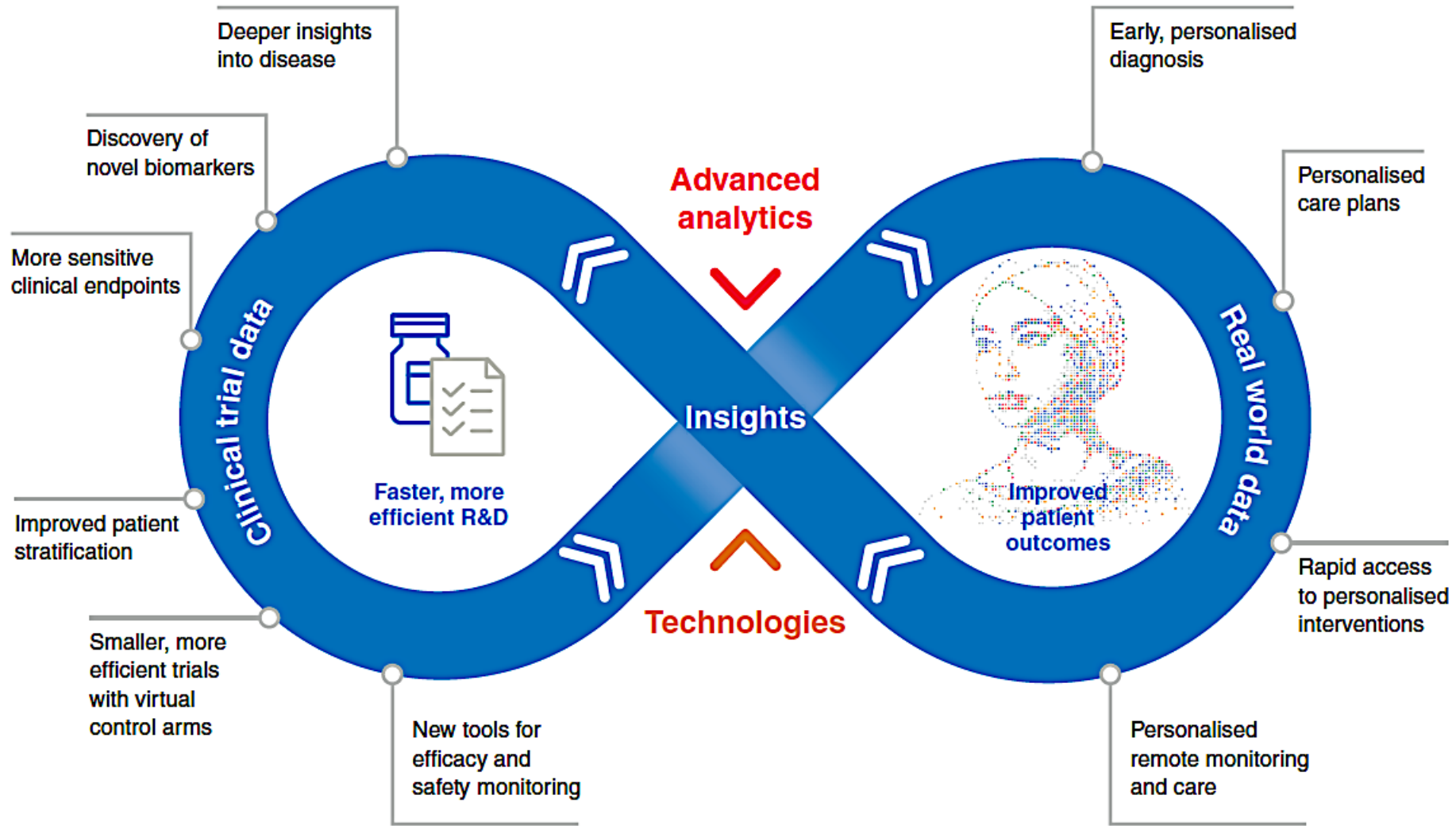


Figure 1. The vision of personalised healthcare: data, technology and analytics provide deeper insights into disease to accelerate research and development and improve patient outcomes.

The Future of Cancer Care

- **Information Technology Revolution**
 - Big Data, Artificial Intelligence, EMR, Digital follow-up, etc.
- **Personalized Care based on deeper genomic analysis/technology**
 - CRISPR - gene-editing, mutation-independent cellular programs, etc.
- **Improvements in Therapy**
 - *Immunotherapy will continue to evolve*
 - Cell Therapies (CAR-T)
 - Combinations, patient selection, predictive biomarkers
 - Microbiome
 - *Therapy based on Monoclonal Antibodies Derivatives*
 - Bi-specific antibodies
 - New Antibody-Drug conjugates
 - Combinations
- **Improvements in diagnostics and staging**
 - *Liquid Biopsies and ctDNA diagnostics revolution*
 - Early diagnosis of cancer (may be even Prevention...)
 - Better monitoring of disease evolution

Take Home Messages

- **Beware of complexity!** Substantial heterogeneity is the rule for most prevalent tumors.
- Note that “**genomics and genes do not hold all the answers**” and that cancer biology and evolution allows for a number of yet to be characterized biological intervening and enabling dimensions very likely to be of clinical significance.
- We are just scratching the surface in our understanding of these characteristics.

Take Home Messages

- Personalized Medicine based on mutated drivers is important and rational, but is only **one of the possible strategies**.
- It is **naïve** to think that we will be able to face the totality of the complexity of cancer with a **single strategy**.
- **Combinations are required** and will be the rule...

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