Genómica de cáncer

- Concepto biológico de Cáncer
- Los genes de cáncer y sus mutaciones
- El genoma del cáncer: mutaciones
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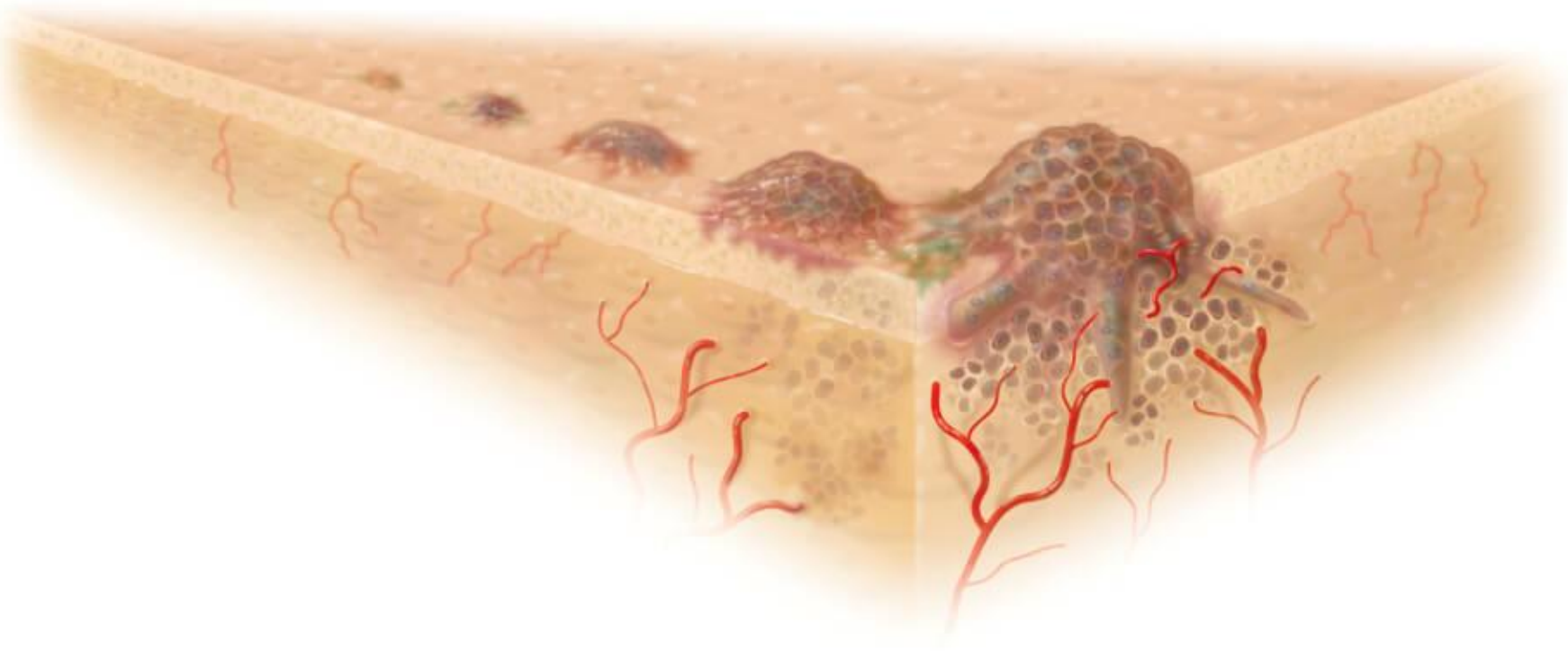
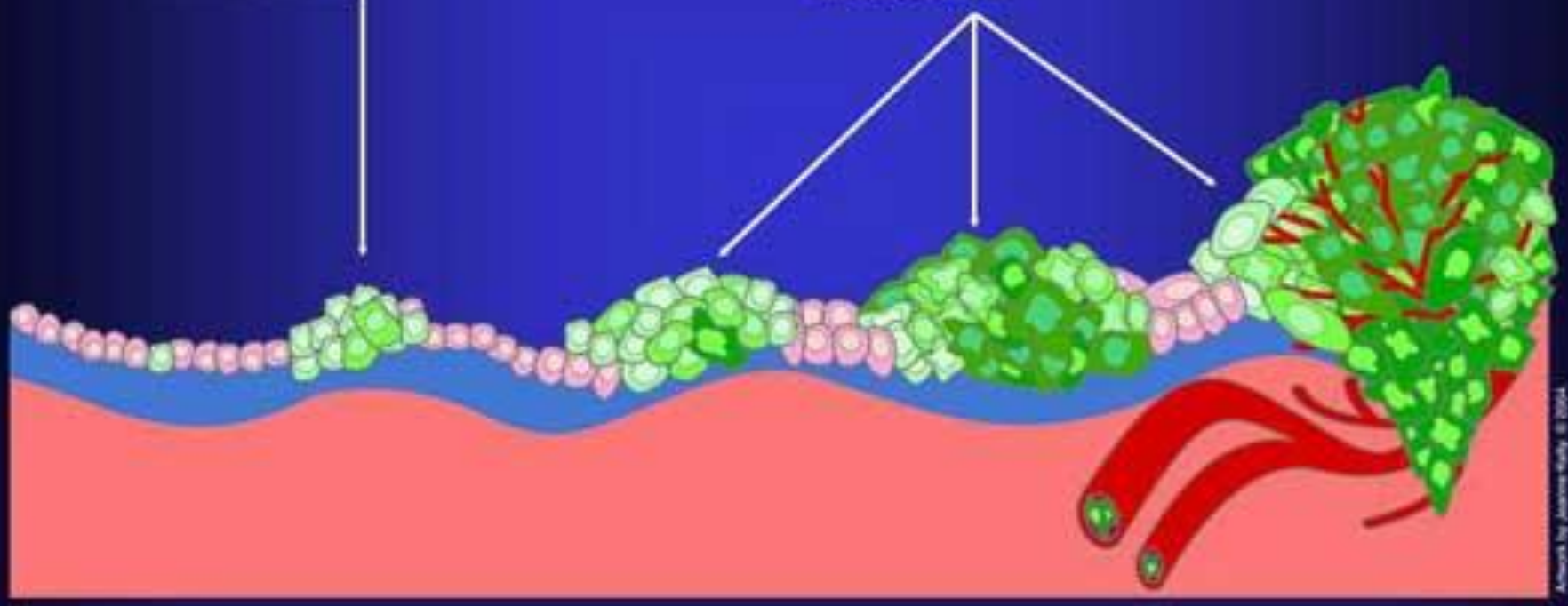
¿Qué es el cáncer?



Los Tumores Malignos comparados con los Benignos

Las células de tumor benignas (no cancerosas) crecen sólo localmente y no se pueden diseminar por invasión o por metástasis

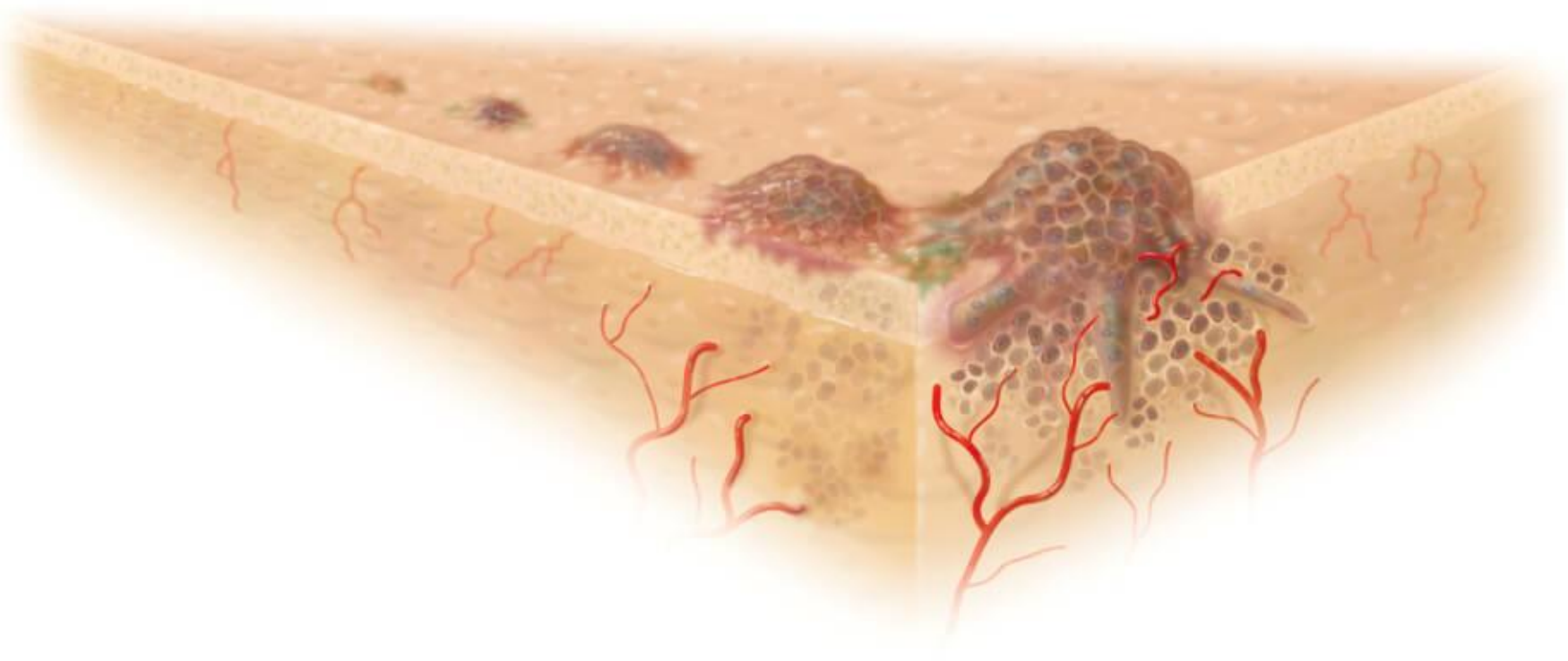
Las células malignas (cancerosas) invaden a los tejidos vecinos, entran a los vasos sanguíneos y se metastatizan a sitios diferentes



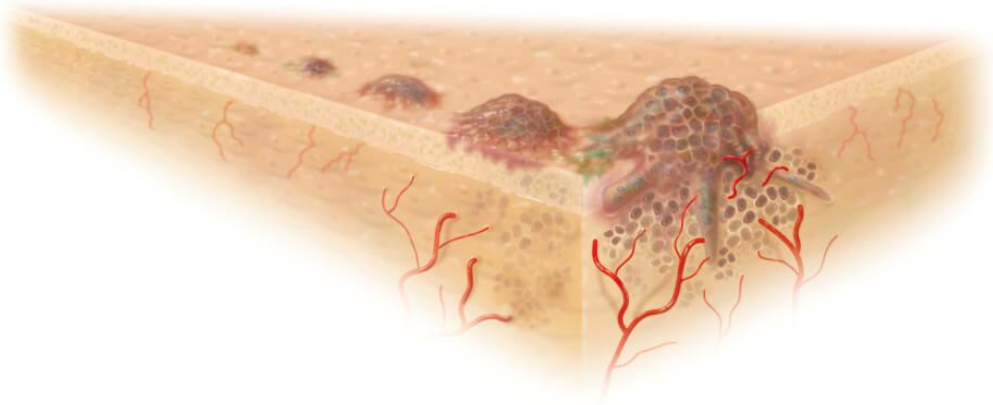
Tiempo

Definición de cáncer

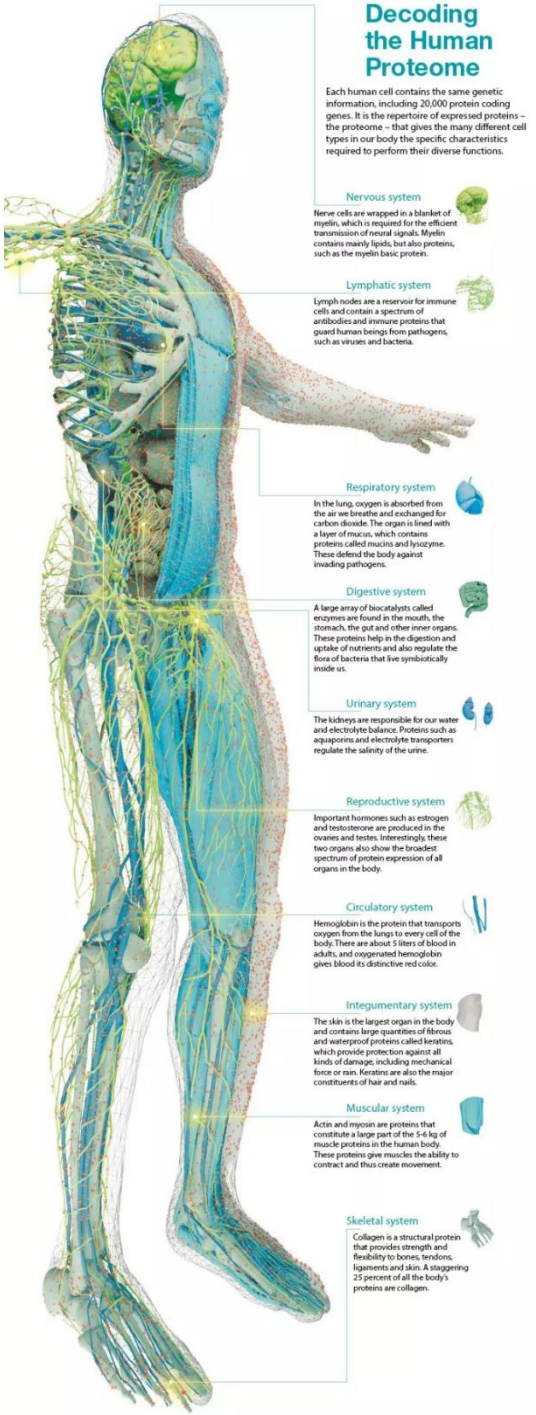
Es una enfermedad provocada por células que comienzan a crecer en forma descontrolada invadiendo tejidos circundates y/o lejanos



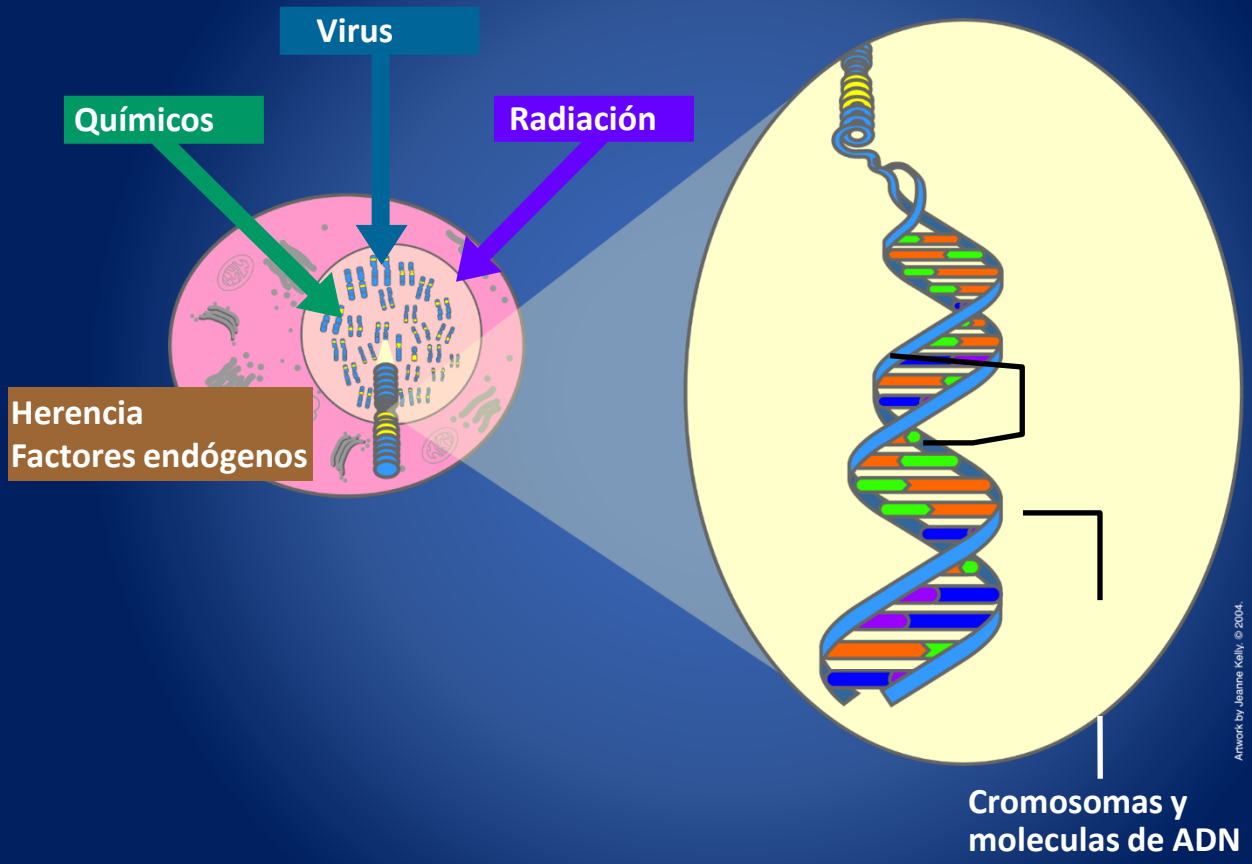
¿ Por qué una célula pierde el control de su crecimiento?



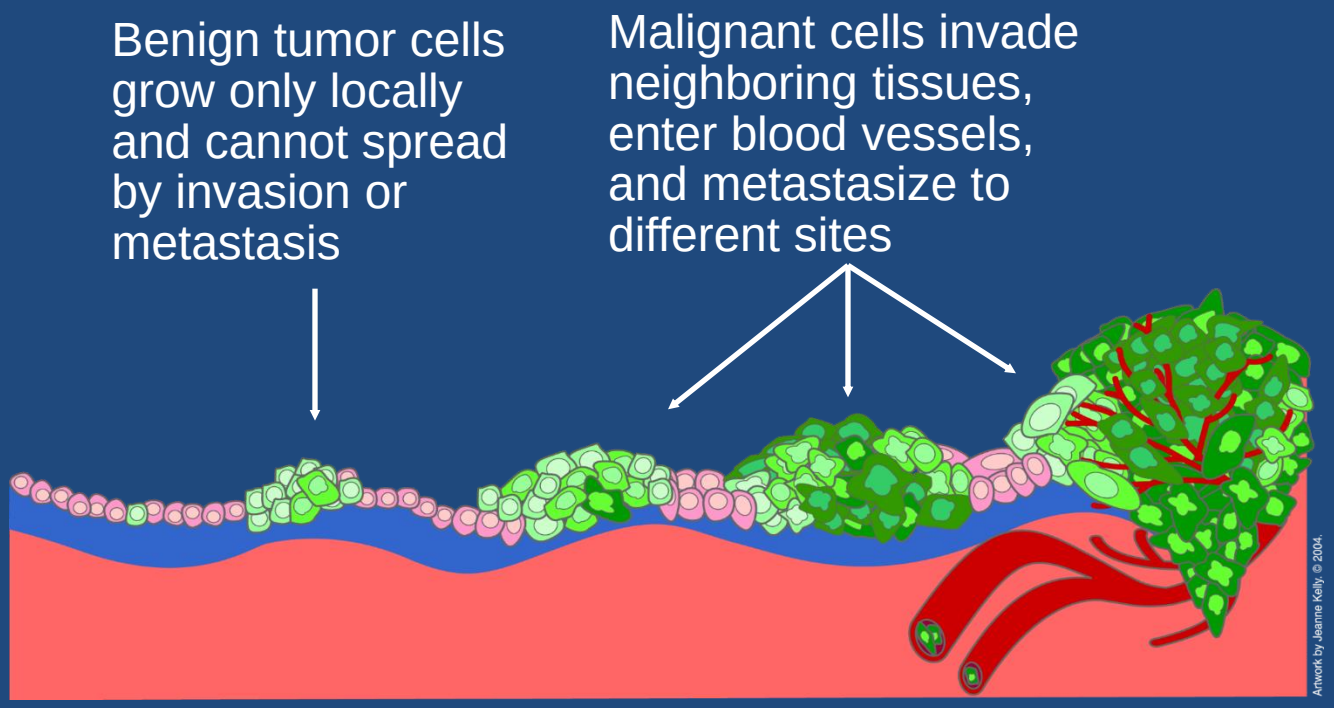
37.2 trilliones de células (3.72×10^{13})
200 tipos celulares diferentes



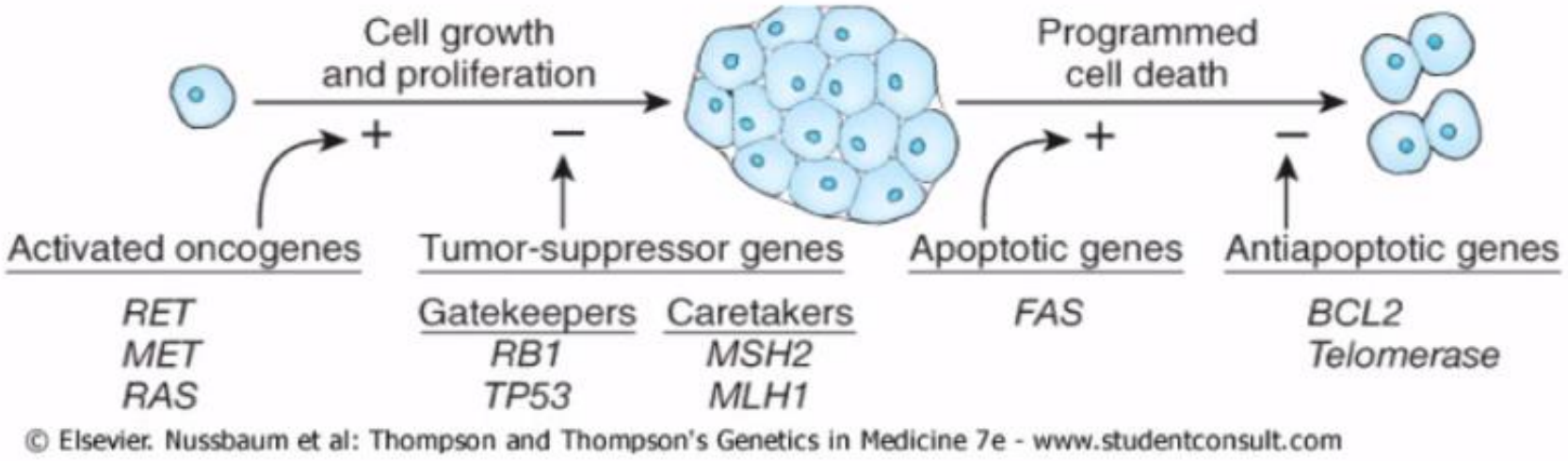
Genes y Cancer



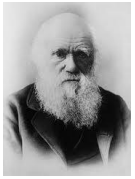
Cancer tiende a involucrar Multiples Mutaciones

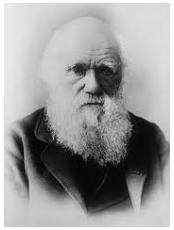


El cáncer es la enfermedad genética más común (afecta células somáticas)



Mutaciones en cáncer afectan procesos biológicos que mejoran la "eficacia reproductiva" de la célula: expansión clonal





Evolución clonal de las células tumorales: Mutación y expansión- MULTIIMPACTO

Mutaciones en cáncer afectan procesos biológicos que mejoran la "eficacia reproductiva" de la célula

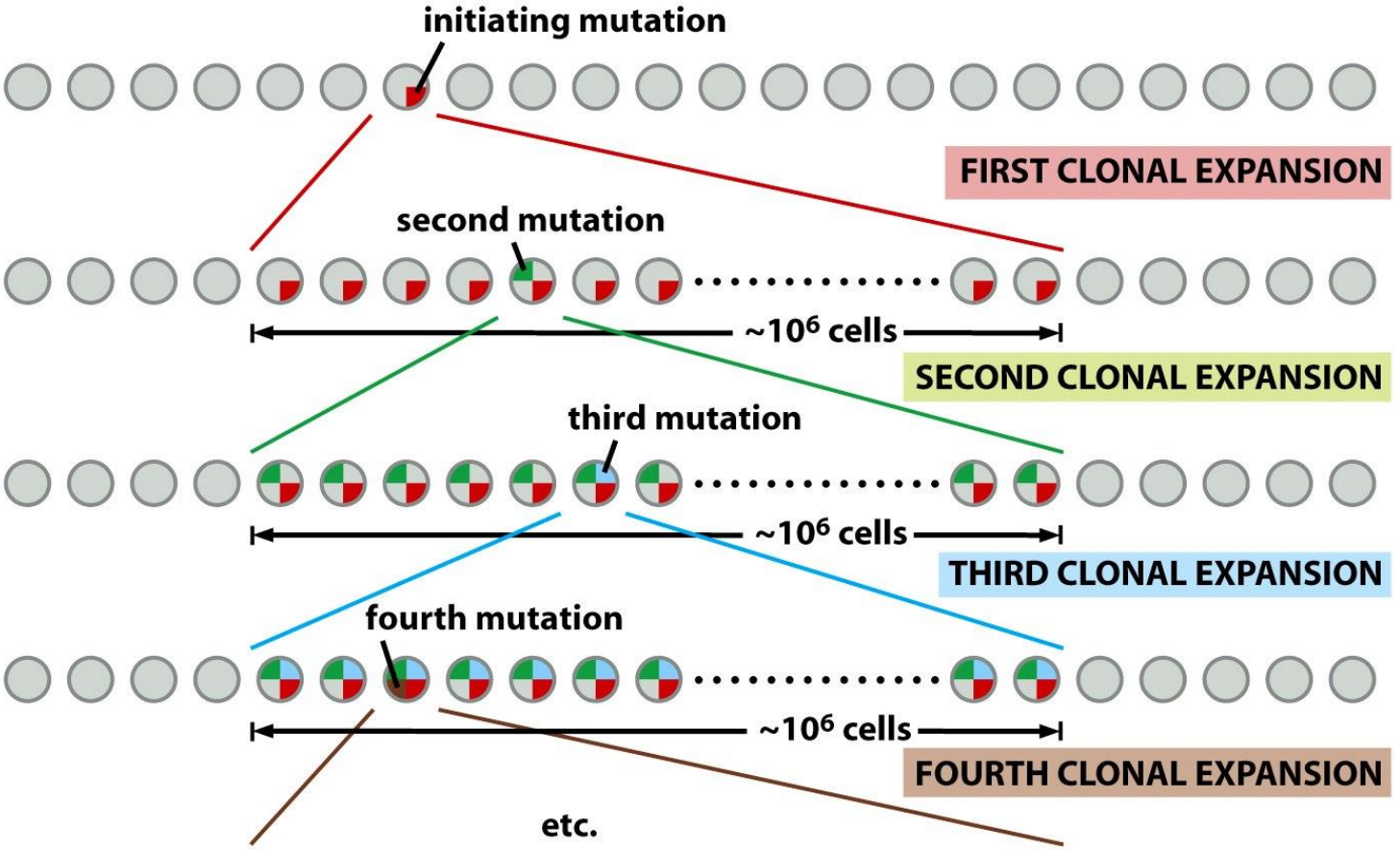
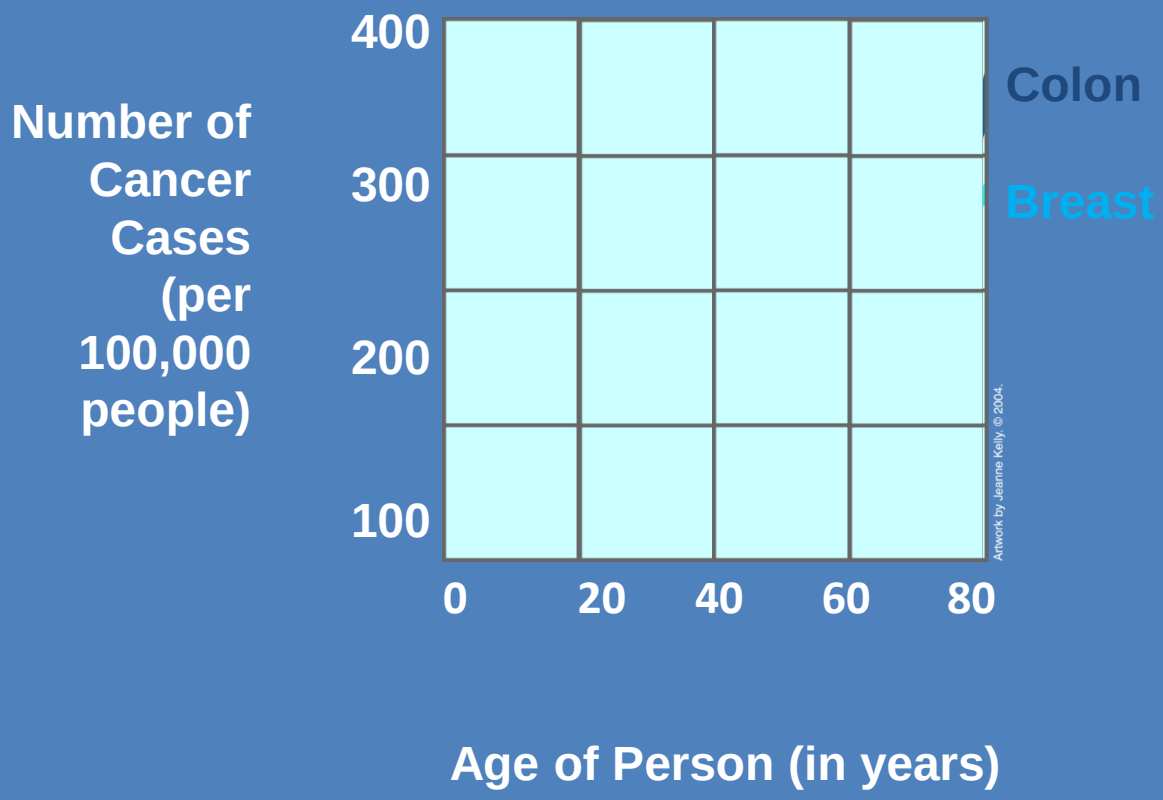
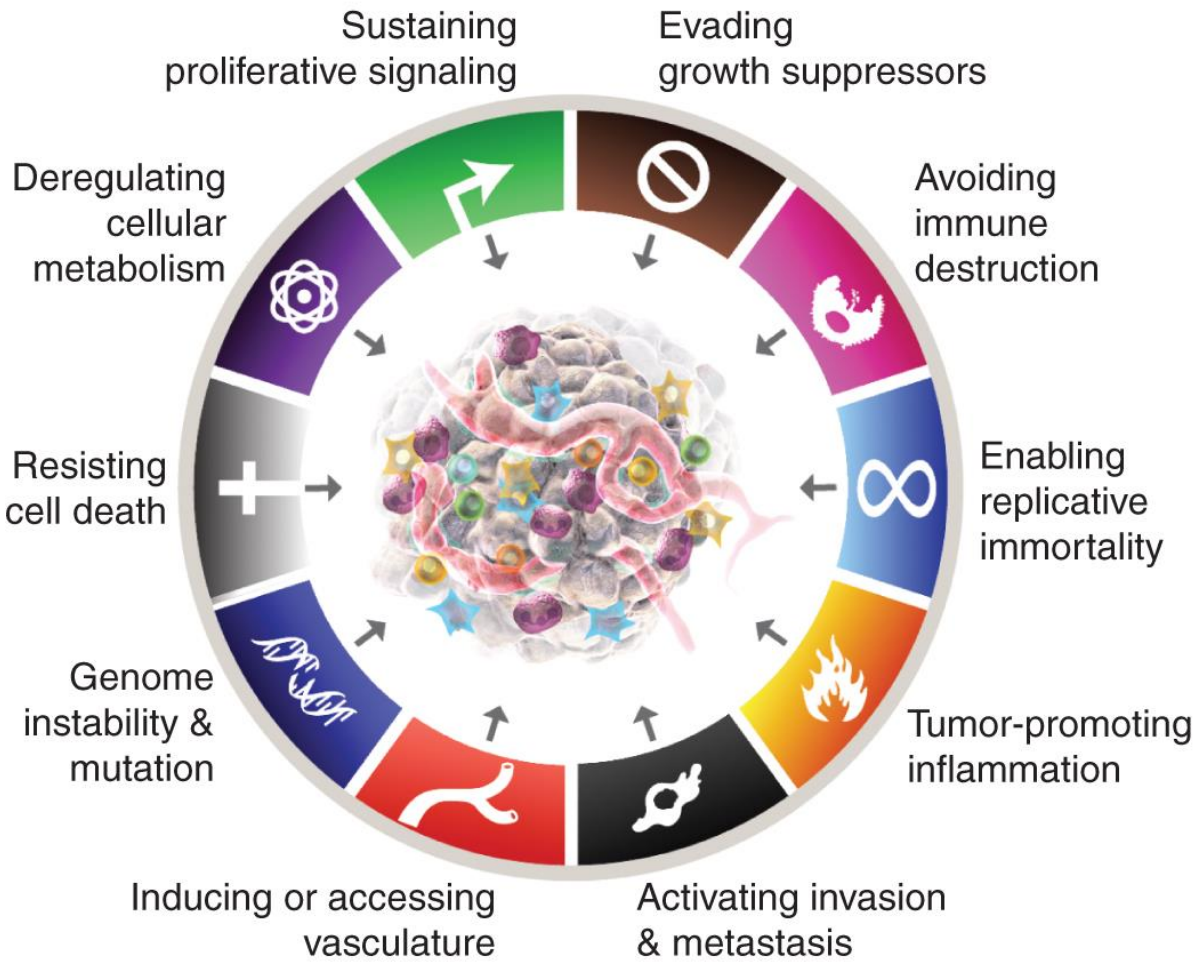


Figure 11.12 *The Biology of Cancer* (© Garland Science 2007)

Edad y Riesgo de Cáncer



Características biológicas del cáncer



AACR American Association for Cancer Research JOURNALS

Cancer Discov. 2022;12(1):31-46. doi:10.1158/2159-8290.CD-21-1059

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ONCOGEN

- Ganancia de función
- Dominante
- Adquirido
- Tardío
- Crecimiento, invasión y angiogénesis
- myc, ras, c-erbB

Activación

- Mutaciones puntuales
- Amplificaciones
- Deleciones/inserciones
- Reordenamientos cromosómicos

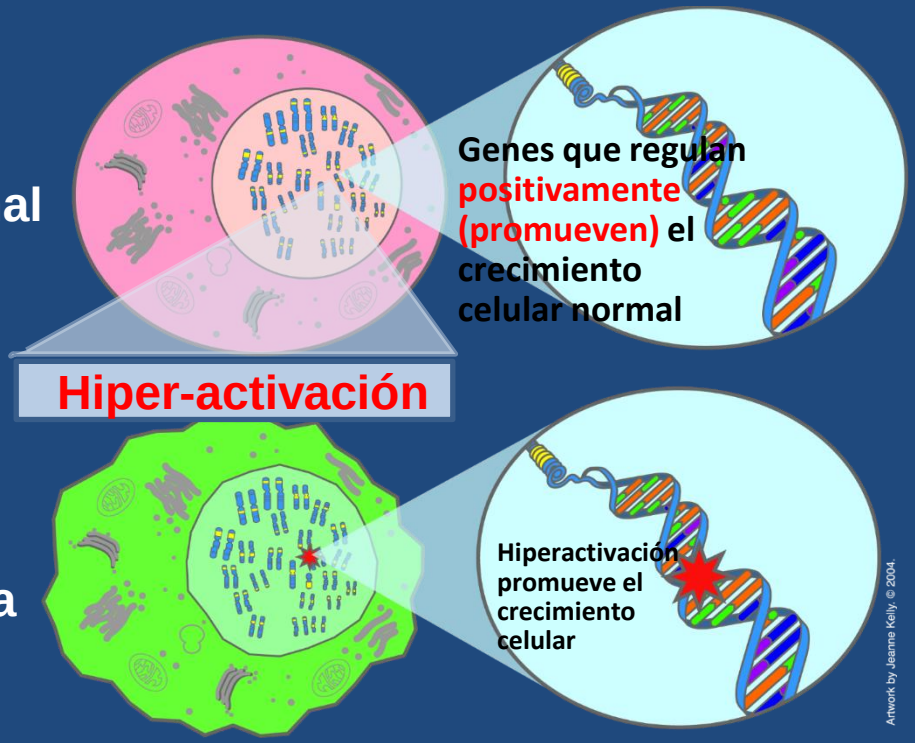
GEN SUPRESOR DE TUMOR

- Pérdida de función
- Recesivo
- Heredado o adquirido
- Temprano
- Aumento de la proliferación y disminución de la reparación
- p53, pRb, p16

Inactivación

- Mutaciones puntuales
- Inserciones/deleciones
- Hipermetilación del promotor: silenciamiento
- Inactivación funcional de la proteína

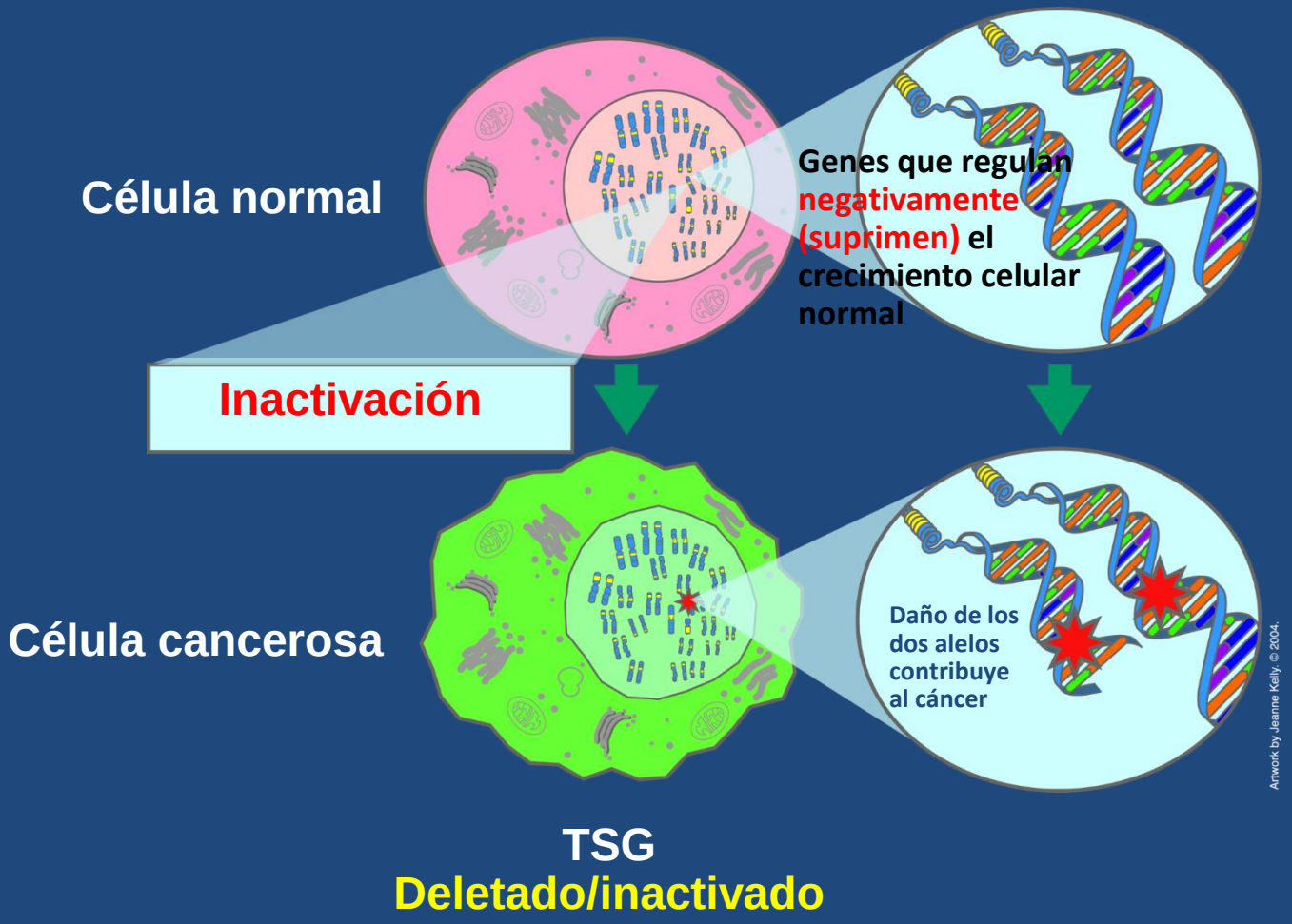
Oncogen (OG)



OG

Duplicado/ Hiperactivado

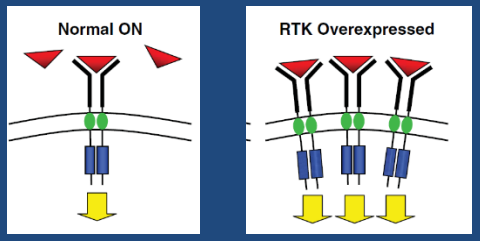
Genes supresores de tumor (TSG)



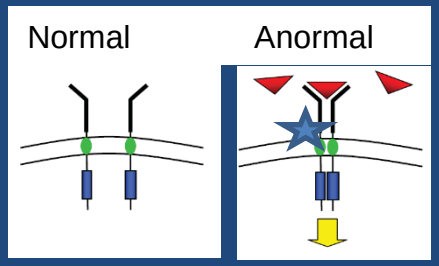
TSG
Deletado/inactivado

Tipos de mutaciones según efecto en la secuencia del ADN

- **ALTERACION DE LA DOSIS :**
  - Amplificación
  - Delección
  - Translocación
  - Metilación



- **ALTERACION DE LA ESTRUCTURA :**
  - Activación
  - Inactivación

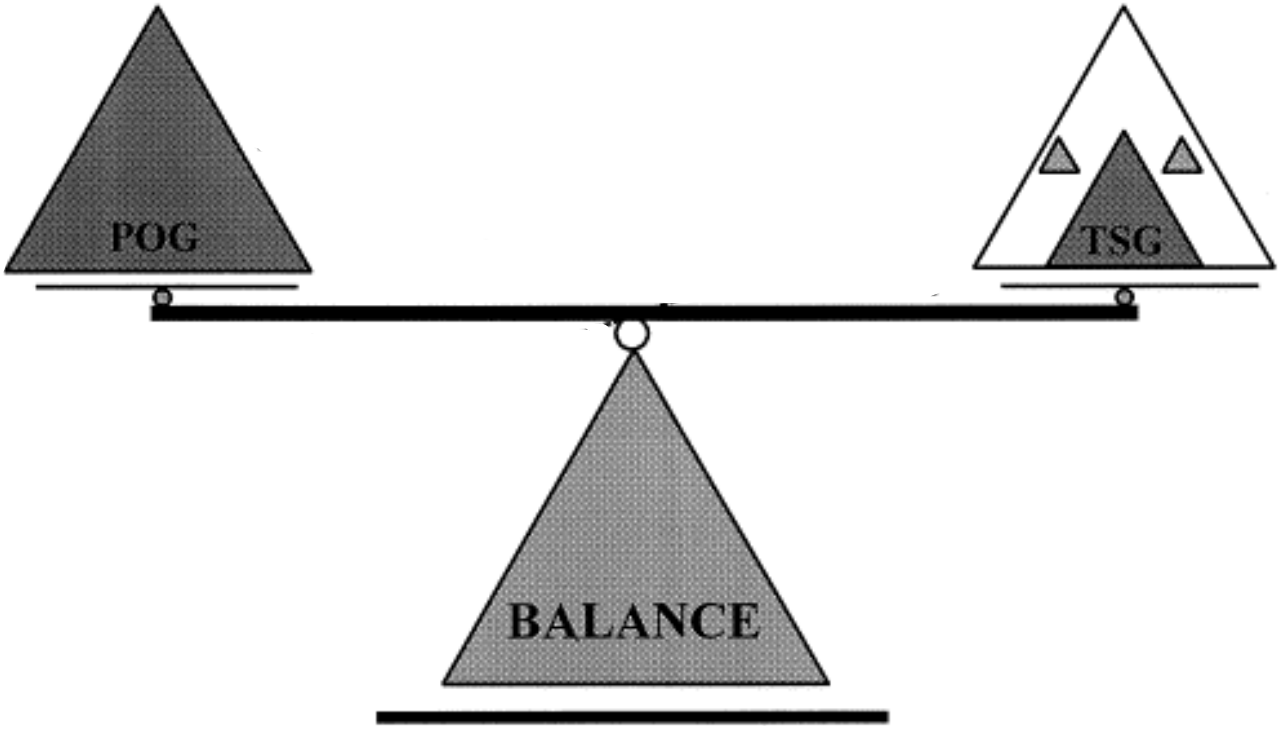


Un efecto similar puede ser causado por ambos tipos de mutaciones.

La desregulación génica en el cáncer:

POG: *proto*-OncoGen

TSG: Tumor Supresor Gen



TIPOS DE MUTACIONES segun su impacto sobre la biología tumoral

(1) Drivers o conductoras: mutaciones que son requeridas para la tumorigenesis.
ventaja selectiva

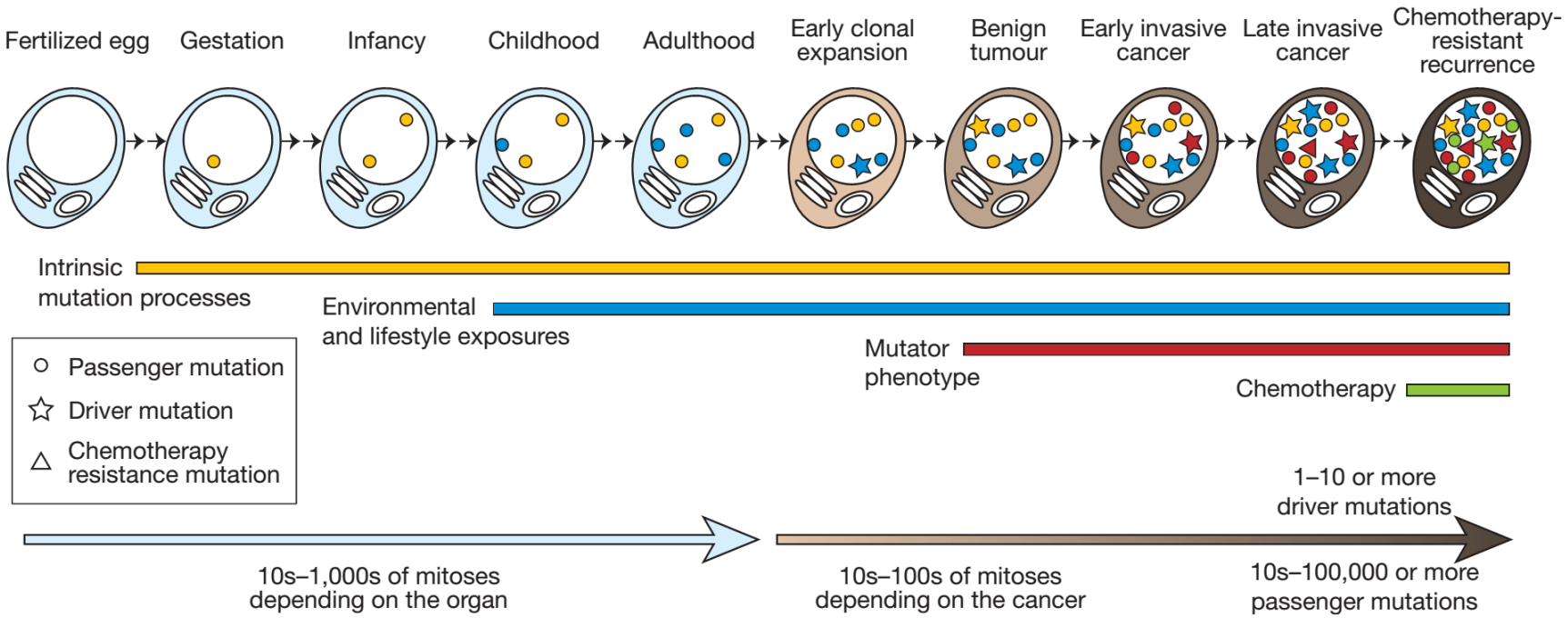
(2) Passengers o pasajeras: mutaciones que ocurren durante la tumorigenesis pero no contribuyen al proceso tumoral neutras

(*3) Mutaciones accionables* Conductoras mas caracterizadas pero también pasajeras.
Confieren suceptibilidad a fármacos

Figure 11.12 *The Biology of Cancer* (© Garland Science 2007)

Evidencia epidemiológica: EDAD

Mutación y expansión en la neoplasia

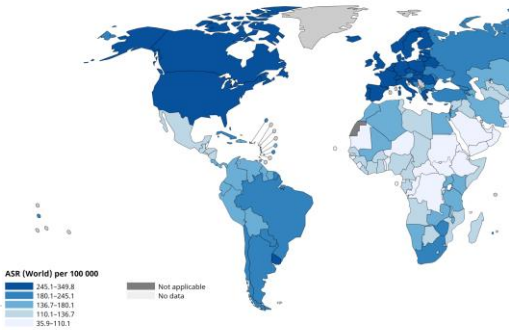


El cáncer es la enfermedad genética más común (afecta células somáticas)

Figure 11.12 *The Biology of Cancer* (© Garland Science 2007)

Evidencia epidemiológica: EDAD

Mortalidad por cáncer en el mundo - 2022



Age-Standardized Rate (World) per 100 000, Mortality, Both sexes, in 2022
All cancers

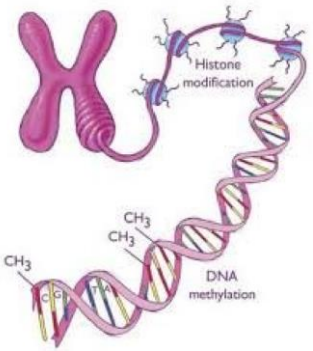
- **20 millones de nuevos casos**
- **9.7 millones de muertes**
- **53.5 millones de personas viviendo con cáncer (a 5 años del diagnóstico)**

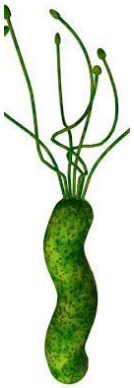
ASR (World) per 100 000
110.3–181.5
93.8–110.3
83.1–93.8
72.4–83.1
25.5–72.4
Not applicable
No data

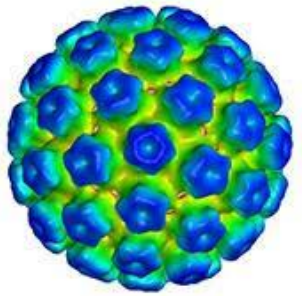
Cancer TODAY | IARC
https://gco.iarc.who.int/today
Data version: Globocan 2022 (version 1.1) - 08.02.2024

International Agency for Research on Cancer
World Health Organization

¿Qué factores aumentan el riesgo de padecer cancer?







Entonces…. ¿es el cáncer una enfermedad GENETICA?

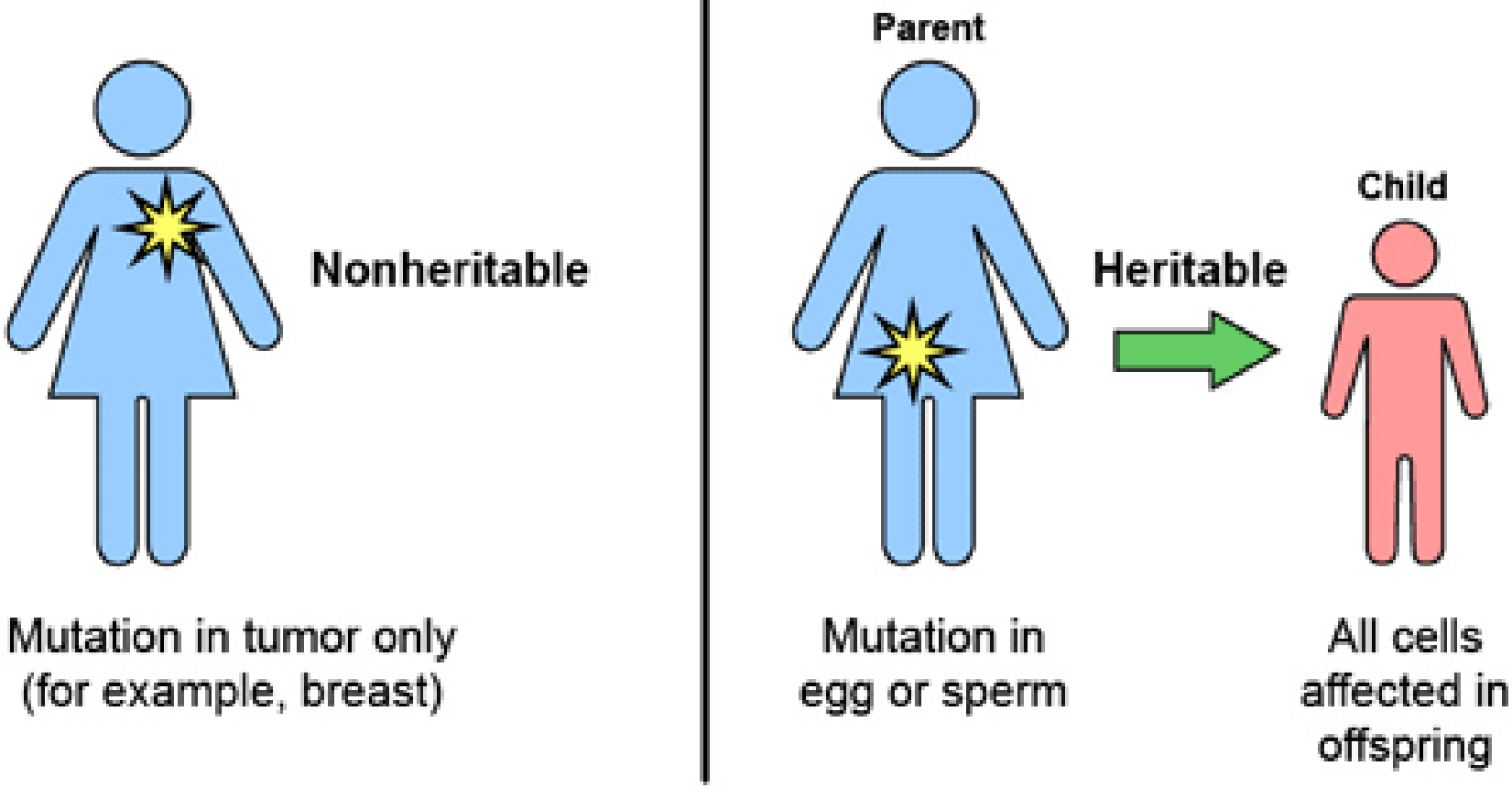
Genético= causado por genes
Heredado=causado por la herencia

Mutaciones Somáticas

Ocurren en tejidos células somáticas
No pueden transmitirse por herencia

Mutaciones Germinales

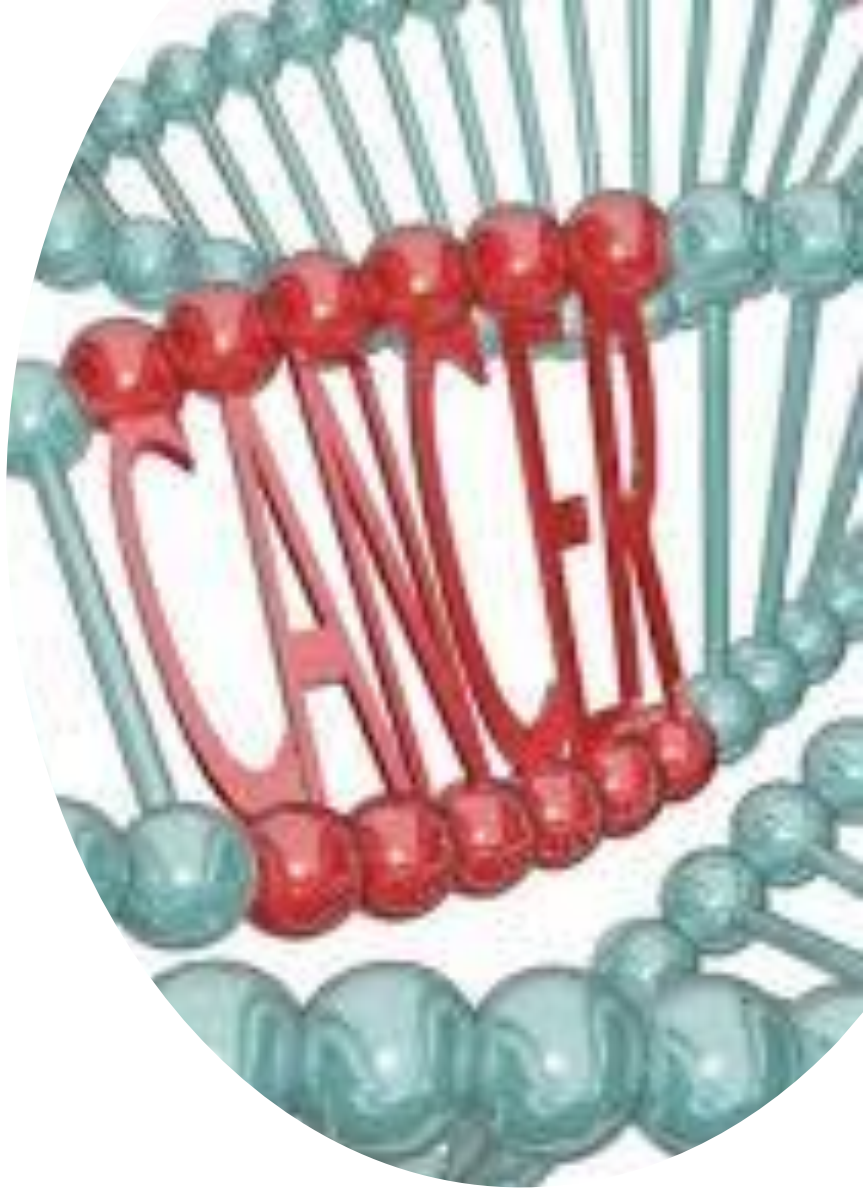
Ocurren en células germinales (gametos)
Pueden ser transmitidas por herencia
Causan síndromes familiares
No pueden transmitirse por herencia



Adapted from the National Cancer Institute and the American Society of Clinical Oncology

La teoría del genética del cáncer

Un tumor es una población de células genéticamente relacionadas que han adquirido la capacidad de proliferar anormalmente.



- **El cáncer es una enfermedad genética mayormente adquirida.**

  Se explica factores ambientales (mutaciones adquiridas/somáticas) y hereditarios (mutaciones heredadas/germinales)

- **Gen de Cáncer: alelo del gen que incrementa el riesgo de cáncer o promueve su desarrollo.**

Adquisición de gen de cáncer:

por herencia (0,1-10%)
por mutaciones somáticas (espontáneas o inducidas por carcinógeno)
por infecciones virales

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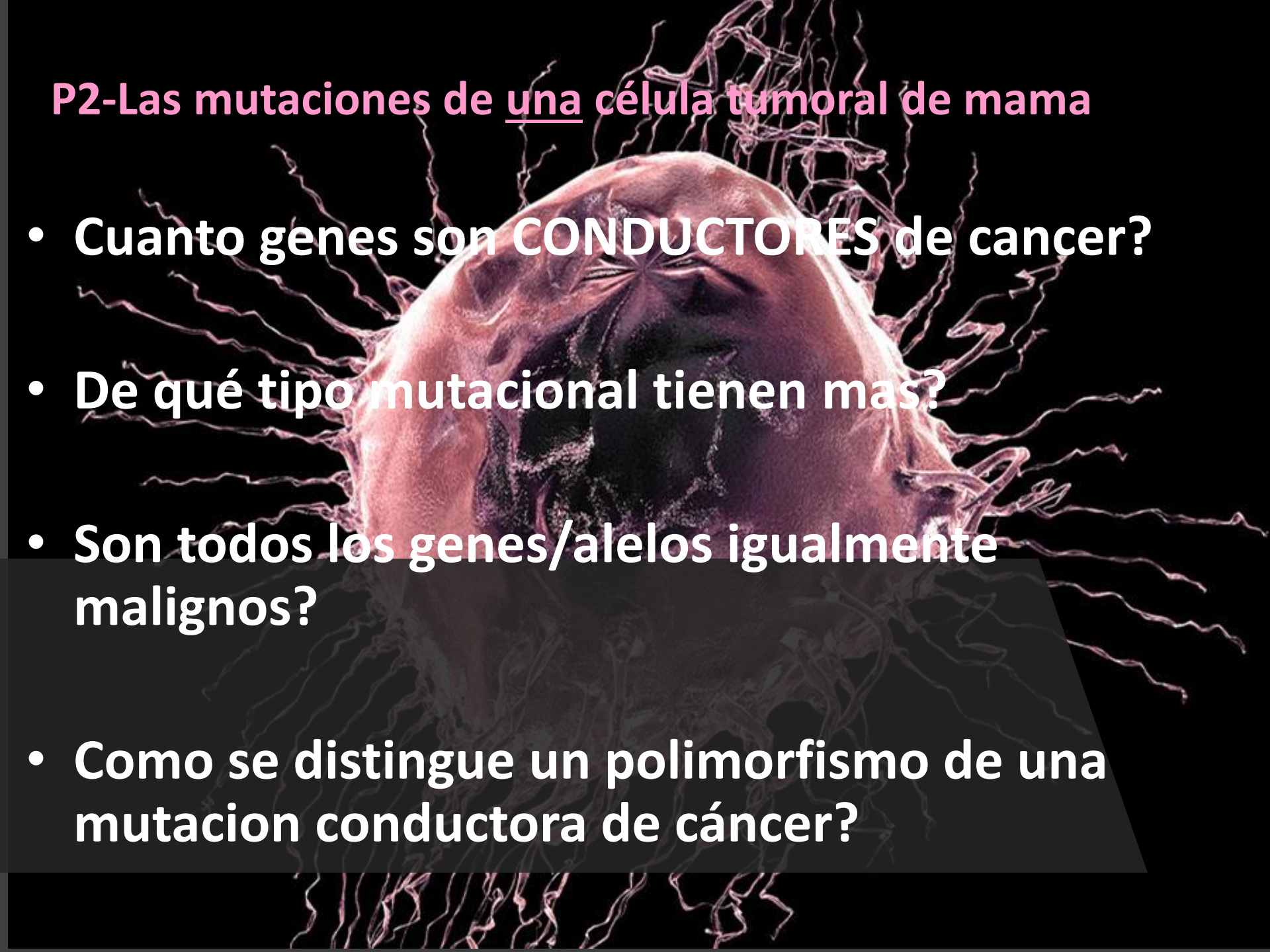


P2-Las mutaciones de una célula tumoral de mama

- Cuanto genes son CONDUCTORES de cancer?
- De qué tipo mutacional tienen mas?
- Son todos los genes/alelos igualmente malignos?
- Como se distingue un polimorfismo de una mutacion conductora de cáncer?

El genoma de una célula tumoral

mutaciones de una célula tumoral

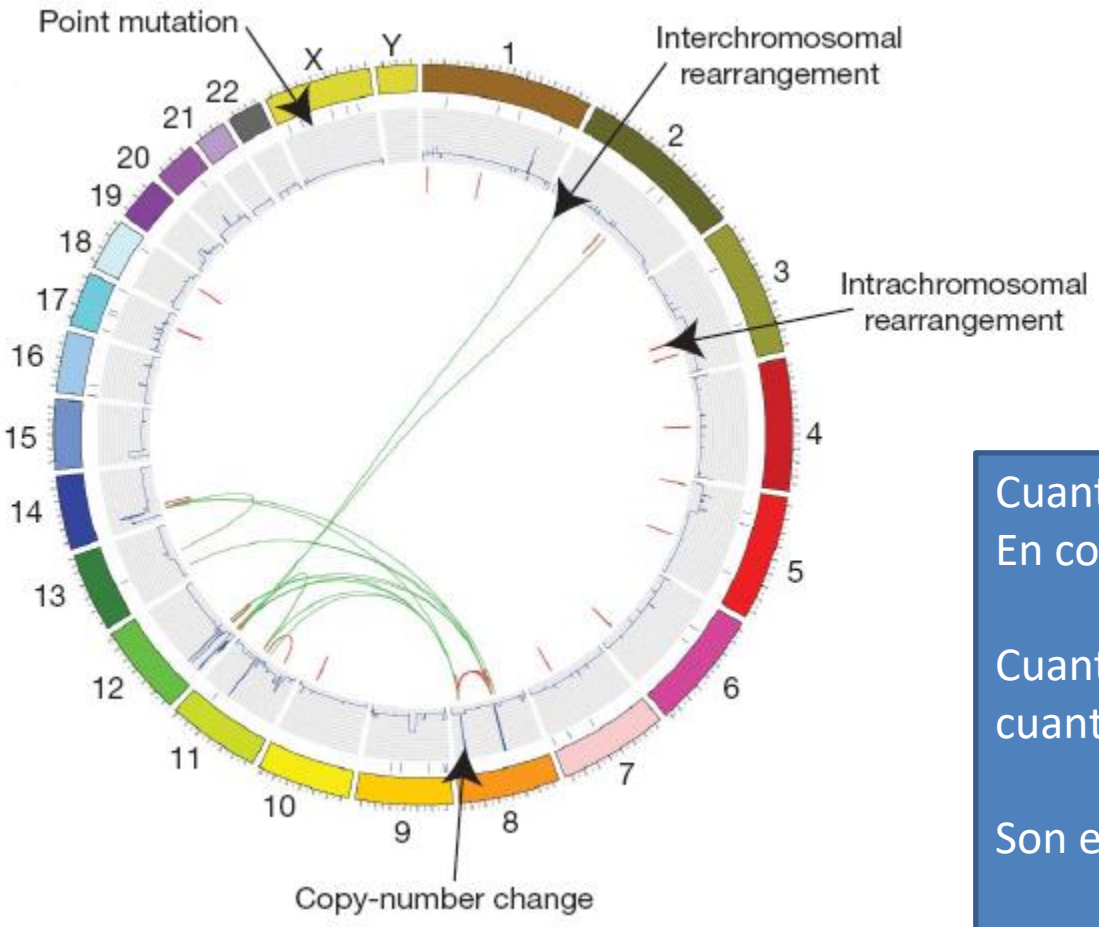


Figure 2 | Figurative depiction of the landscape of somatic mutations present in a **single cancer genome**. Part of catalogue of somatic mutations in the small-cell lung cancer cell line NCI-H2171. Individual chromosomes are depicted on the outer circle followed by concentric tracks for point mutation, copy number and rearrangement data relative to mapping position in the genome. Arrows indicate examples of the various types of somatic mutation present in this cancer genome.

Cuantas mutaciones tiene?
En comparación a qué célula normal?

Cuantas son importantes para neoplasia y cuantas no?

Son exclusivas de SCLC?

Tiene utilidad clínica?

Circos diagram summarizing the full somatic mutation content

http://www.nature.com/nature/journal/v458/n7239/full/nature07943.html

¿Cuántos genes del genoma contribuyen al cáncer?

>1% de todos los genes humanos están implicados en por vía mutacional en cancer.

90% have somatic mutations in cancer

20% bear germline mutations that predispose to cancer

10% show both somatic and germline mutations.

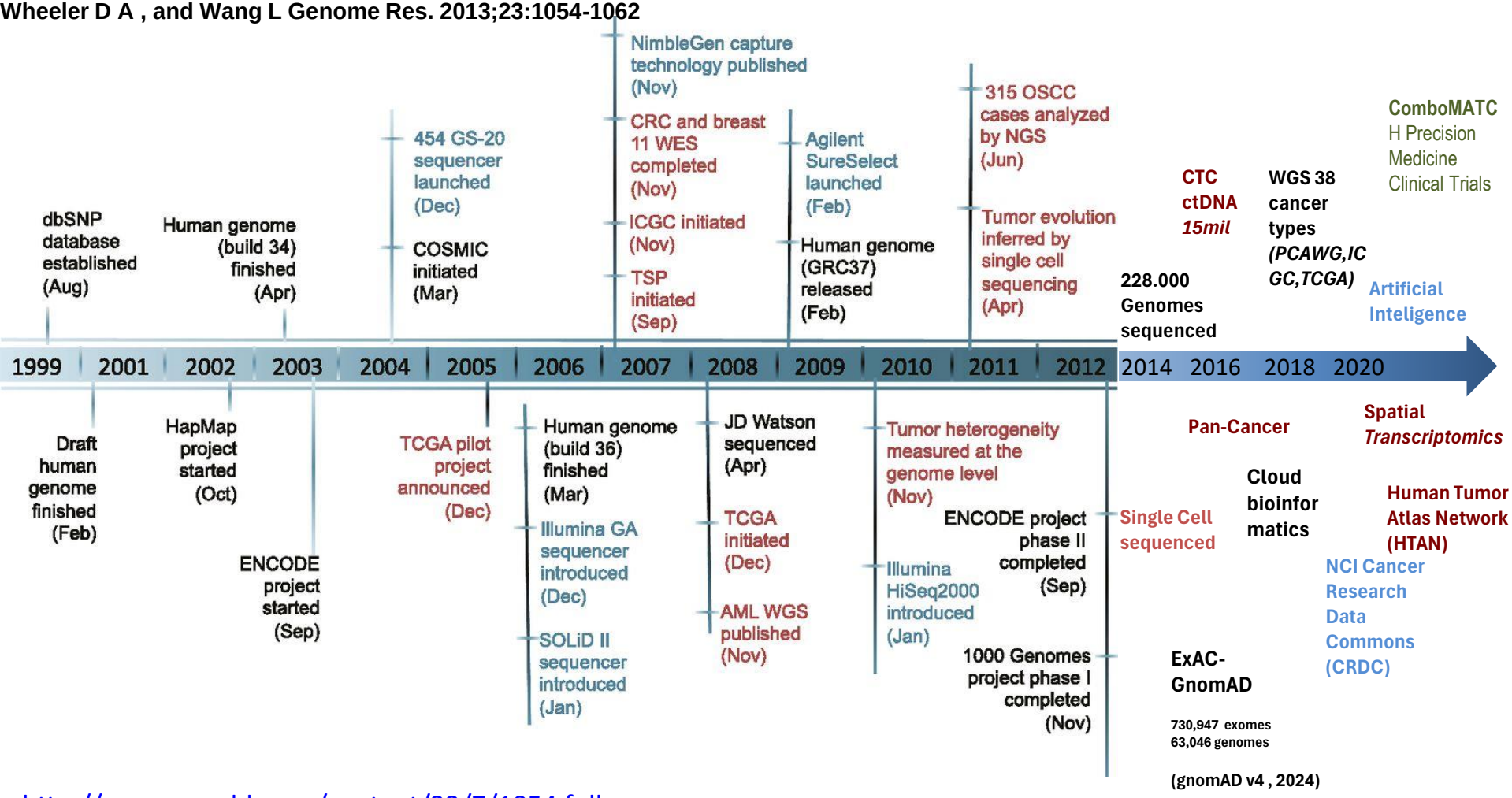
El Cancer Gene Census es un esfuerzo en curso para catalogar los genes cuya mutación ha sido causalmente implicada en cancer.

hoy: **748**

http://cancer.sanger.ac.uk/cancergenome/projects/census/

Principales hitos en Génómica de Cáncer

Wheeler D A , and Wang L Genome Res. 2013;23:1054-1062



http://genome.cshlp.org/content/23/7/1054.full

https://link.springer.com/article/10.1007/s10555-021-09969-z

Research Areas

- Cancer Biology Research
- Cancer Genomics Research
- Research on Causes of Cancer
- Cancer Prevention Research
- Screening & Early Detection
- Cancer Diagnosis Research
- Cancer Treatment Research
- Cancer & Public Health
- Cancer Disparities
- Childhood Cancers Research
- Global Cancer Research

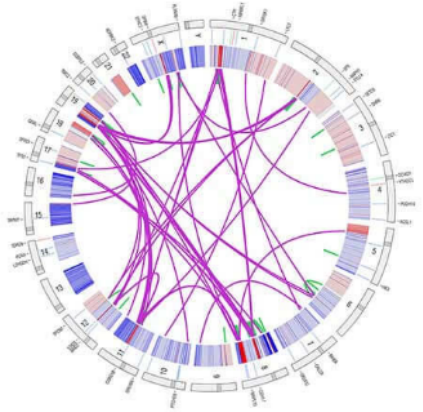
Cancer Genomics Research

ON THIS PAGE

The Importance of Cancer Genomics Research

The study of cancer genomes (all the DNA in cancer cells) has revealed the mind-boggling complexity of genomic changes that drive cancer growth and survival. This knowledge has greatly expanded our understanding of how cancer develops and progresses. Ultimately, it has led to new ways of diagnosing and treating cancer, as well as new ways of identifying those at high risk of developing cancer. In short, genomics research has changed the way we see cancer.

Large-scale research projects such as The Cancer Genome Atlas (TCGA), and its pediatric counterpart Therapeutically Applicable Research to Generate Effective Treatments (TARGET), have surveyed and cataloged the genomic changes in multiple types of cancer. The discovery of novel



This Circos plot visualizes data from The Cancer Genome Atlas (TCGA) and allows scientists to explore the interrelationships among different data points.
Credit: National Cancer Institute

http://www.cancer.gov/research/areas/genomics#3

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Center for Cancer Genomics

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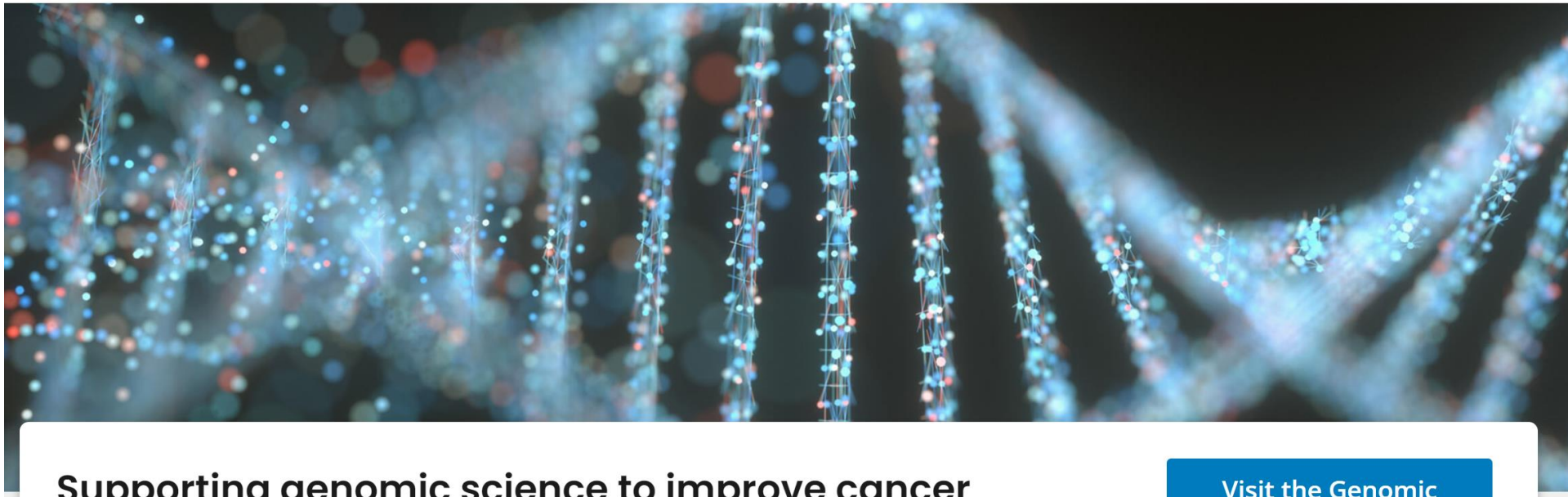
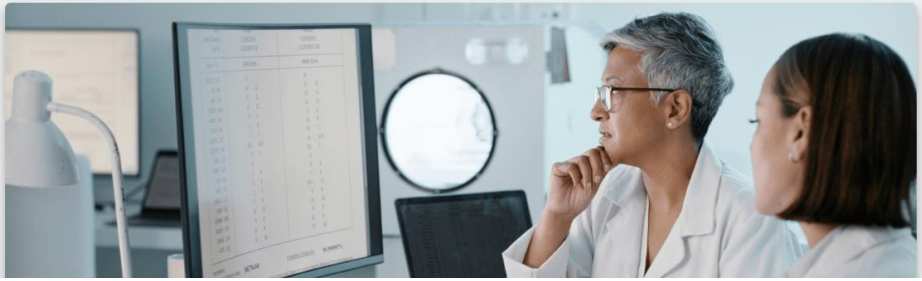


Supporting genomic science to improve cancer diagnosis, treatments, and outcomes

Visit the Genomic Data Commons

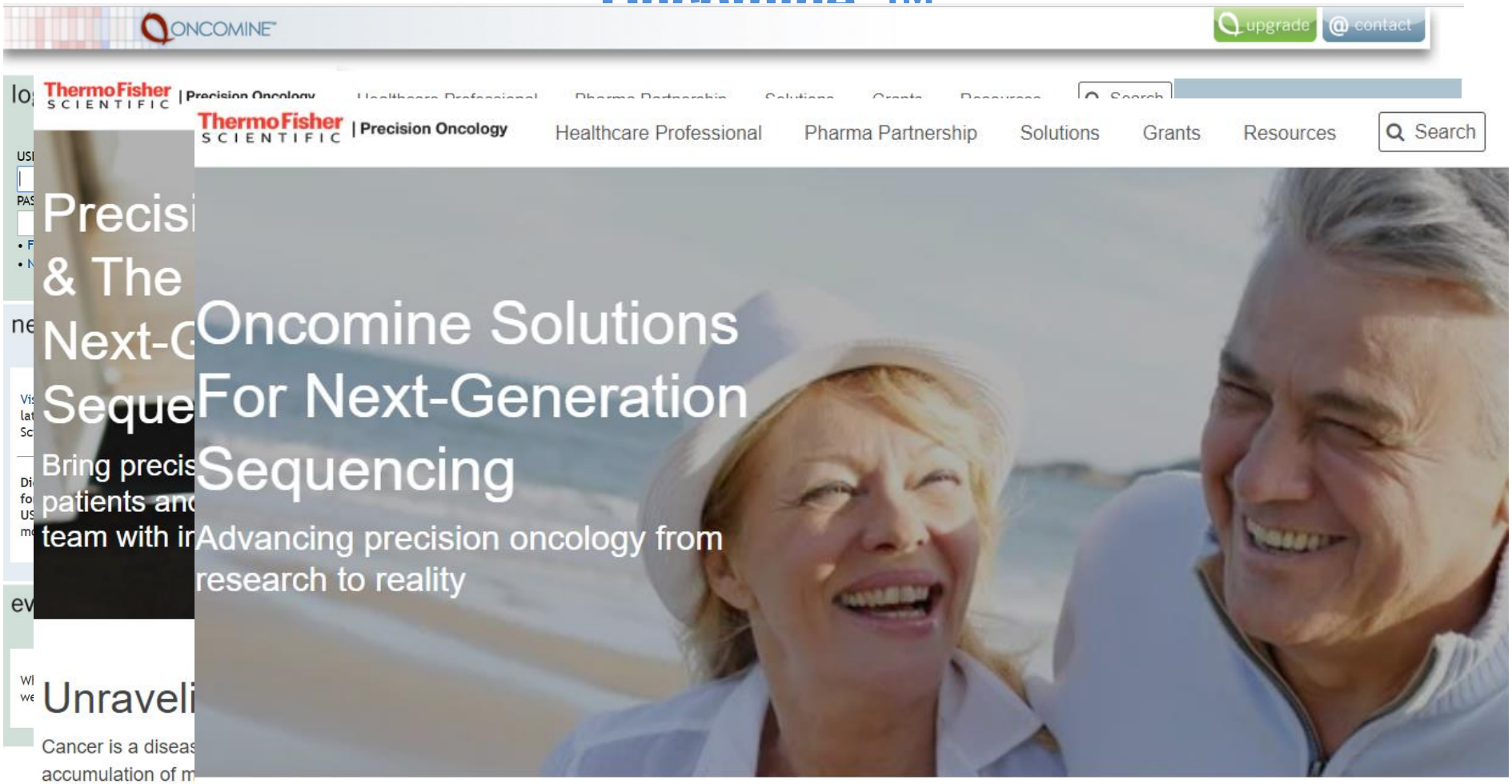
Explore Research Programs



CCG Data and Resources

https://www.cancer.gov/ccg/

Oncomine™

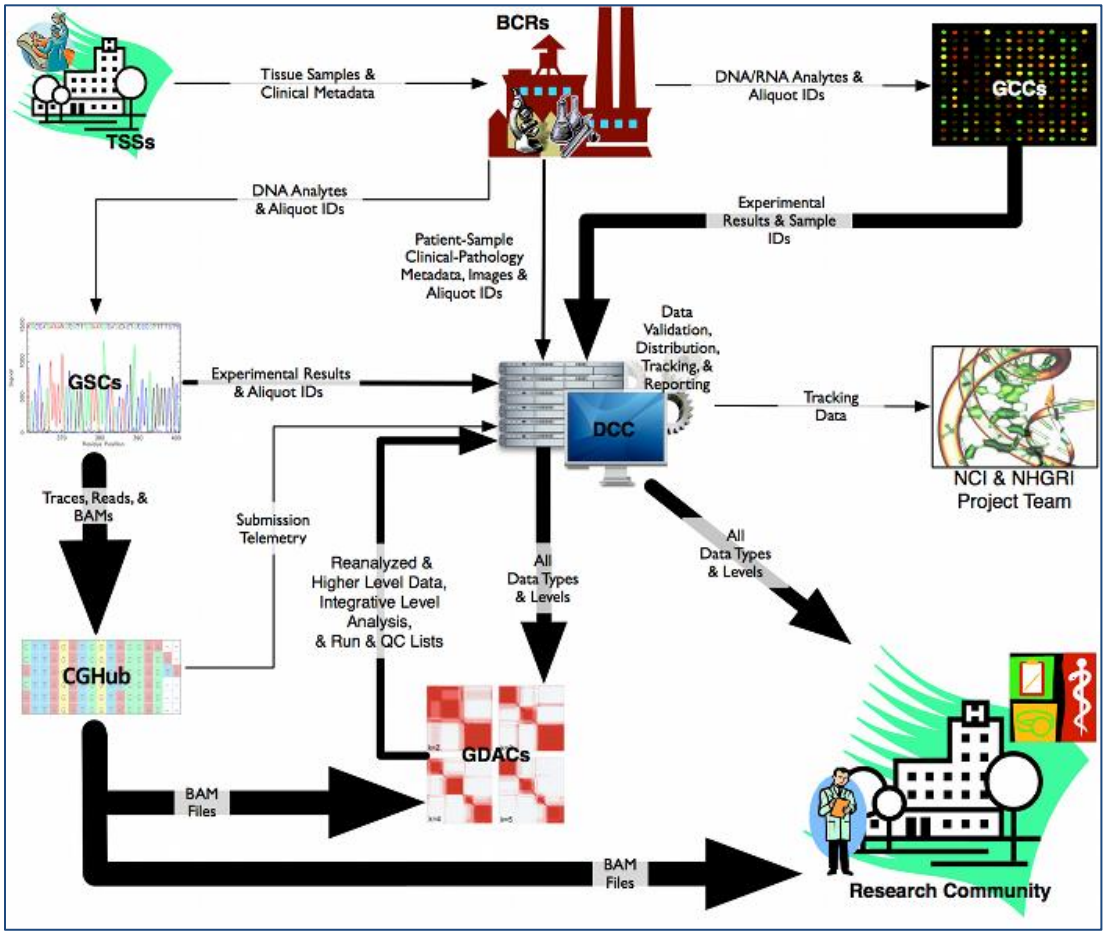


Because Cancer Won't Wait.

Because this fight needs the latest technology and most insightful answers. That's why we created Oncomine Solutions, an integrated next-generation sequencing-based approach carefully designed for oncology labs—easy to implement and easy to use. Now any hospital can bring the power of Oncomine Solutions to their in-house laboratory, provide molecular insights to inform the most critical decisions, and realize the promise of precision oncology.

https://www.oncomine.org/resource/login.html

The Cancer Genome Atlas (TCGA)



The flow of TCGA data and biospecimen products.

Clinical Information
Specimens
SAMPLE type
Tumor normal
Sequence data: Genomic, Transcriptomic, Proteomic, smallRNAs, CHIP-Seq, Meth-Seq

Tipos de datos ómicos de cancer

¿Qué molécula?

DNA GENOMES : Sequence (genome, exome, gene panel, ecDNA)

Copy number, DNA subset (total, free circulating or Ct cell, signature)

EPIGENOMES (chromatin accessibility –DNAseI/ATAC-seq), chromatin marks –histones- DNA methylation patterns)

RNA Transcriptomes: totalRNA /mRNA / small RNAs /molecular signature

Selected RNA pools (protein bound, sub-celular location, biotype, modified)

PROTEIN Total cell or selected pool (membrane, free circulating,)

¿Qué tecnología?

- *DNA sequencing (DNAseq) -SNP, CNV, LOH*
- *SNP-based platforms*
- *Array-based DNA methylation sequencing*
- *RNA sequencing (RNAseq)*
- *smallRNA sequencing (miRNAseq)*
- *Reverse-phase protein array (RPPA)*
- *ATAC-seq, CHIP-seq*
- *Single cell sequencing*

¿Qué muestra?

- Normal/Disease/Sub-type, Primary/Metastasis/Treatment Resistant, Body Fluids
- Tissue, Circulating cells, circulating cell free
- Tumor bulk, single cell, spatial organized single cell
- Response to a perturbation (chemotherapy, immunotherapy, radiotherapy)

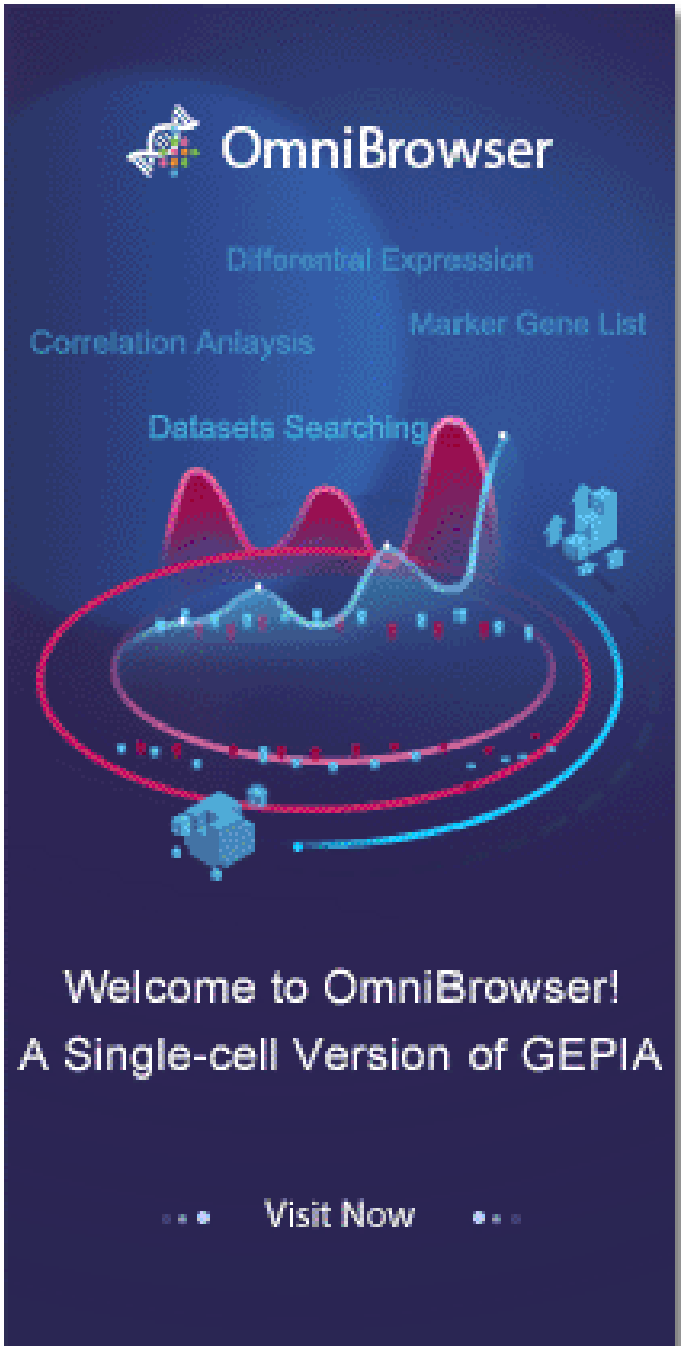
Repositorios, Visualización y análisis de datos genómicos/clínicos de cáncer

- The Cancer Imaging Archive, TCIA (http://www.cancerimagingarchive.net)
- Berkeley Morphometric Visualisation and Quantification from H&E sections (http://tcga.lbl.gov/biosig/tcgadownload.do)
- The Cancer Digital Slide Archive, CDSA(http://cancer.digitalslidearchive.net/)
- Cancer Genome Workbench, CGWB (https://cgwb.nci.nih.gov/)
- UCSC XENA Browser (http://xena.ucsc.edu/getting-started/)
- Integrative Genomics Viewer, IGV(http://www.broadinstitute.org/igv)
- The cBioPortal for Cancer Genomics (http://cbioportal.org)
- Regulome Explorer (http://explorer.cancerregulome.org/)
- SRA Sequence Read Archive (https://www.ncbi.nlm.nih.gov/sra)
- Catalogue of somatic mutations in cancer (http://www.sanger.ac.uk/science/tools/cosmic)

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4322527/

GEPIA

GEPIA



https://omnibrowser.abiosciences.com/?from=gepia#/user/login?redirect=%2F

NCI launches cloud-based cancer genomics data platform

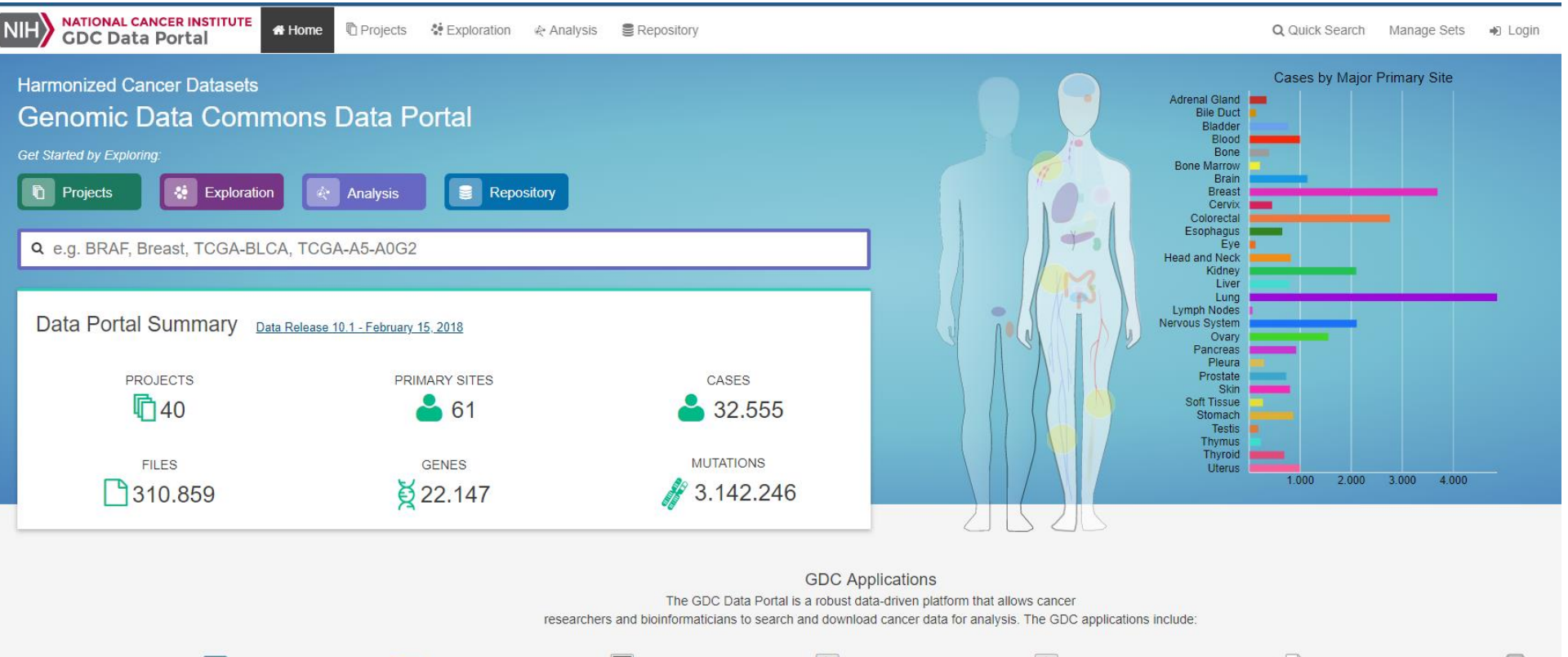
By Chase Gunter Jun 08, 2016

The National Cancer Institute announced the opening of the Genomic Data Commons, a publicly accessible database that allows researchers to access, analyze and upload genomic data to advance cancer research.

The GDC, built and managed by the University of Chicago Center for Data Intensive Science, harmonizes cancer data from 12,000 patient records and makes it available

TCGA analysis tools

GDC Portal
cBioPortal
Xena
ACE



cBioPortal FOR CANCER GENOMICS

Data Sets | Web API | R/MATLAB | Tutorials | FAQ | News | Visualize Your Data | About

The cBioPortal for Cancer Genomics provides **visualization**, **analysis** and **download** of large-scale **cancer genomics** data sets.
Please cite Gao et al. *Sci. Signal.* 2013 & Cerami et al. *Cancer Discov.* 2012 when publishing results based on cBioPortal.

QUERY | DOWNLOAD DATA

Select Studies: **0** studies selected (**0** samples) Select all Search...

What's New @cbioportal

cBioPortal
@cbioportal
The next phase of the cBioPortal architecture upgrade is complete: The Cancer Types Summary and Mutual Exclusivity pages have been updated.

QUERY | DOWNLOAD DATA

Select Studies: **0** studies selected (**0** samples) Select all Search...

Lymph	5
Other	3
Ovary/Fallopian Tube	3
Pancreas	9
Peripheral Nervous System	1
Pleura	2
Prostate	13
Skin	10
Soft Tissue	3
Testis	1

Prostate

Prostate Adenocarcinoma

Genomic Hallmarks of Prostate Adenocarcinoma (CPC-GENE, Nature ...	477 samples
MSK-IMPACT Clinical Sequencing Cohort in Prostate Cancer (MSK, JC...	504 samples
Metastatic Prostate Cancer, SU2C/PCF Dream Team (Robinson et al., ...	150 samples
Neuroendocrine Prostate Cancer (Trento/Cornell/Broad 2016)	114 samples
Prostate Adenocarcinoma (Broad/Cornell, Cell 2013)	57 samples
Prostate Adenocarcinoma (Broad/Cornell, Nat Genet 2012)	112 samples
Prostate Adenocarcinoma (Fred Hutchinson CRC, Nat Med 2016)	176 samples
Prostate Adenocarcinoma (MSKCC, Cancer Cell 2010)	216 samples
Prostate Adenocarcinoma (TCGA, Cell 2015)	333 samples
Prostate Adenocarcinoma (TCGA, Provisional)	499 samples
Prostate Adenocarcinoma CNA study (MSKCC, PNAS 2014)	104 samples
Prostate Adenocarcinoma Organoids (MSKCC, Cell 2014)	12 samples
Prostate Adenocarcinoma, Metastatic (Michigan, Nature 2012)	61 samples

Cancer Cell Line Encyclopedia (Novartis/Broad, Nature 2012) Query this study Download data

Cancer Cell Line Encyclopedia from the Broad Institute and Novartis, containing 883 samples; raw data at the CCLE. PubMed

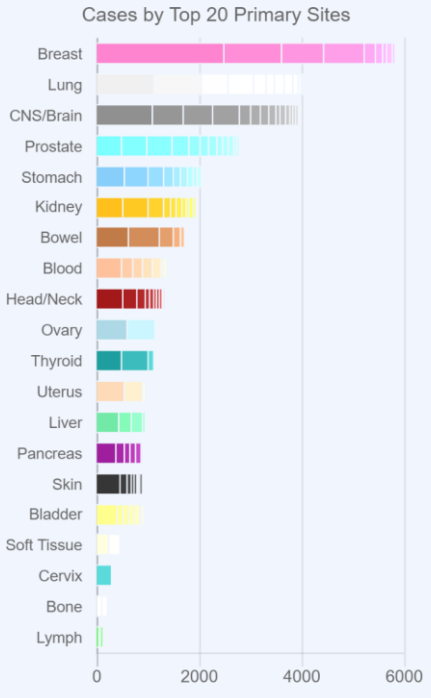
Study Summary | Clinical Data | Mutated Genes

Show / Hide Columns (11) | Choose Fixed Columns (2) | DATA | COPY | Showing 8 samples (filtered from 1019) Reset | Input a keyword

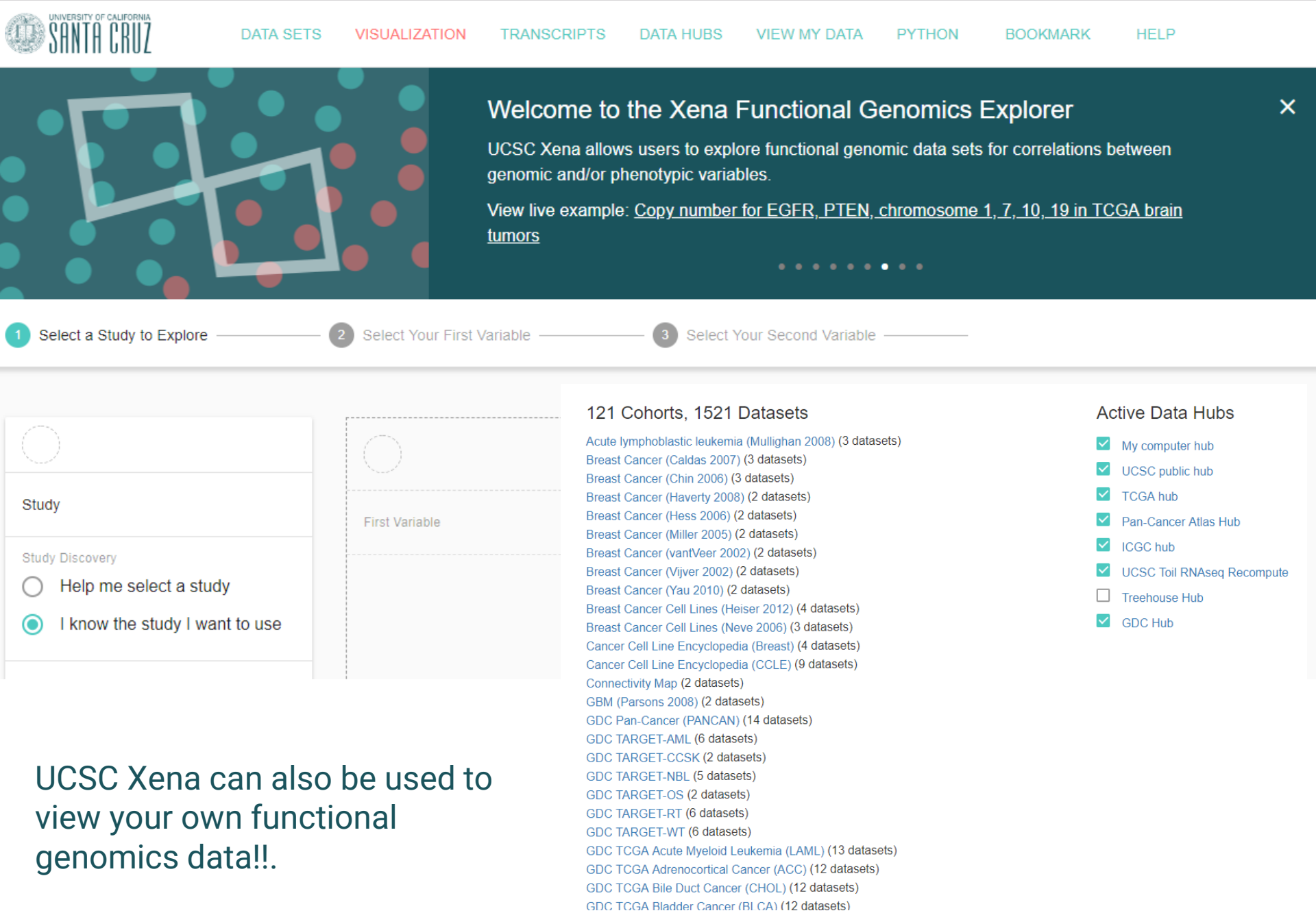
Filter column	prostate	Filter column	Filter column	Filter column	Filter column
Patient ID	**Sample ID**	**Cancer Studies**	**Cancer Type**	**Cancer Type Deta...**	**Data Source**
22Rv1	22RV1_PROSTATE	cellline_ccle_broad	Cancer of Unknown P...	Mixed Cancer Types	ATCC
DU_145	DU145_PROSTATE	cellline_ccle_broad	Cancer of Unknown P...	Mixed Cancer Types	ATCC
LNCaP_clone_FGC	LNCAPCLONEFGC_P...	cellline_ccle_broad	Cancer of Unknown P...	Mixed Cancer Types	ATCC
MDA_PCa_2b	MDAPCA2B_PROSTATE	cellline_ccle_broad	Cancer of Unknown P...	Mixed Cancer Types	ATCC
NCI-H660	NCIH660_PROSTATE	cellline_ccle_broad	Cancer of Unknown P...	Mixed Cancer Types	ATCC
PC-3	PC3_PROSTATE	cellline_ccle_broad	Cancer of Unknown P...	Mixed Cancer Types	ATCC
PRECLH_PROSTATE	PRECLH_PROSTATE	cellline_ccle_broad	Cancer of Unknown P...	Mixed Cancer Types	NA
VCaP	VCAP_PROSTATE	cellline_ccle_broad	Cancer of Unknown P...	Mixed Cancer Types	ATCC

Cancer Studies

The portal contains 166 cancer studies (details)



Memorial Sloan Kettering Cancer Center (MSK).



UCSC Xena can also be used to view your own functional genomics data!!.

https://xenabrowser.net/heatmap/

https://www.biorxiv.org/content/early/2018/05/18/326470

COSMIC

Overview

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Publications

Overview

COSMIC, the "Catalogue Of Somatic Mutations In Cancer" is an expert-curated database encompassing the wide variety of somatic mutation mechanisms causing human cancer (http://cancer.sanger.ac.uk). Growing in both content and scope, COSMIC holds details on millions of mutations across thousands of cancer types. Hand-curation of key cancer genes (selected from the Cancer Gene Census) provide in-depth detail on mutation distributions and effects, whilst semi-automated curation of cancer genomes provides broad somatic annotations toward target discovery and identification of patterns and signatures. This information is fully available via website or download, updated every three months.

Curation

25,000 peer reviewed papers

Cancer Gene Census : This is a list of hundreds of genes with substantial published evidence in oncology. Necessarily conservative, this is a very high-confidence list based on good-quality publications. Selection of high-impact genes from this list for curation drives COSMIC.

COSMIC : Upon selection of a gene from the Census for full expert curation, all papers mentioning its mutation in human cancer are collected and exhaustively curated before it is released into a new version of COSMIC. Once this initial curation is released, the gene is updated as significant new information is published. Each curator is responsible for a defined set of 60 or more genes, developing substantial expertise. In parallel, cancer genomes are curated via a more bioinformatic approach. Genomic data is obtained in standard formats; roughly half is from published supplementary information tables, and the other half from genome consortia such as TCGA, ICGC. Standard pipelines (eg Ensembl VEP) annotate these genomic data in genic terms for COSMIC release. Such molecular profiling includes point mutations, gene fusions, copy number annotations, structural breakpoints, gene expression and CpG island methylation variants.

32,000 genomes

Cancer Cell Lines Project : The Cell lines Project in COSMIC is an effort to fully profile over 1000 cell lines regularly used in cancer research; annotations include exome sequencing, CNV and gene expression profiling, RNASeq and CpG methylation. This information is maintained in a separate, but parallel system alongside COSMIC and regularly updated to highlight the most valuable information across the cell line panel.

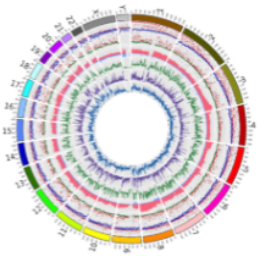
GDSC: Genomics of Drug Sensitivity in Cancer

We have undertaken high-throughput screening of drug sensitivity for >1,000 cancer cell lines across hundreds of potential therapeutic compounds. We have matched the drug sensitivity data to genomic, epigenomic and transcriptomic characterisation of the cell lines. This datatset is available for browsing or download.

Tool type

- Database software

Screenshots



Related Tools

- Cancer Gene Census

  The *Cancer Gene Census* is a high-confidence list of genes with substantial published evidence in Oncology.

- Cancer Genome Browser

Showing 1 to 25 of 733 entries

COSMIC v100, released 21-MAY-24

COSMIC, the Catalogue Of Somatic Mutations In Cancer, is the world's largest and most comprehensive resource for exploring the impact of somatic mutations in human cancer.

Start using COSMIC by searching for a gene, cancer type, mutation, etc. below.

eg Braf, COLO-829, Carcinoma, V600E, BRCA-UK, Campbell SEARCH

Projects

COSMIC is divided into several distinct projects, each presenting a separate dataset or view of our data:

COSMIC
The core of COSMIC, an expert-curated database of somatic mutations

Cell Lines Project
Mutation profiles of over 1,000 cell lines used in cancer research

COSMIC-3D
An interactive view of cancer mutations in the context of 3D structures

Cancer Gene Census
A catalogue of genes with mutations that are causally implicated in cancer

Cancer Mutation Census
Classification of genetic variants driving cancer

Actionability
Mutations actionable in precision oncology

Data curation

- Gene Curation — details of our manual curation process
- Gene Fusion Curation — details of our curation process for gene fusions
- Genome Annotation — information on the annotation of genomes
- Drug Resistance — curation of mutations conferring drug resistance
- Mutational Signatures — a census of mutation signatures in cancer
- Actionability — Mutations actionable in precision oncology

COSMIC News

Follow @cosmic_sanger

Largest genomic cancer resource accelerating research and drug development

Press release COSMIC has released the 100th version of its knowledgebase, containing further information on 300,000 somatic mutations linked to human cancers. More...

'You can't be what you can't see': Inspiring inclusion with Nidhi Bindal Dhir, COSMIC Head of IT

International Women's Day 2024 is focused on inspiring inclusion. We are privileged at COSMIC to work with a range of incredible women such as our Head of IT Nidhi Bindal Dhir who we caught up with to reflect on her 15 years as part of the team! More...

Curation in context: A glimpse into COSMIC v99

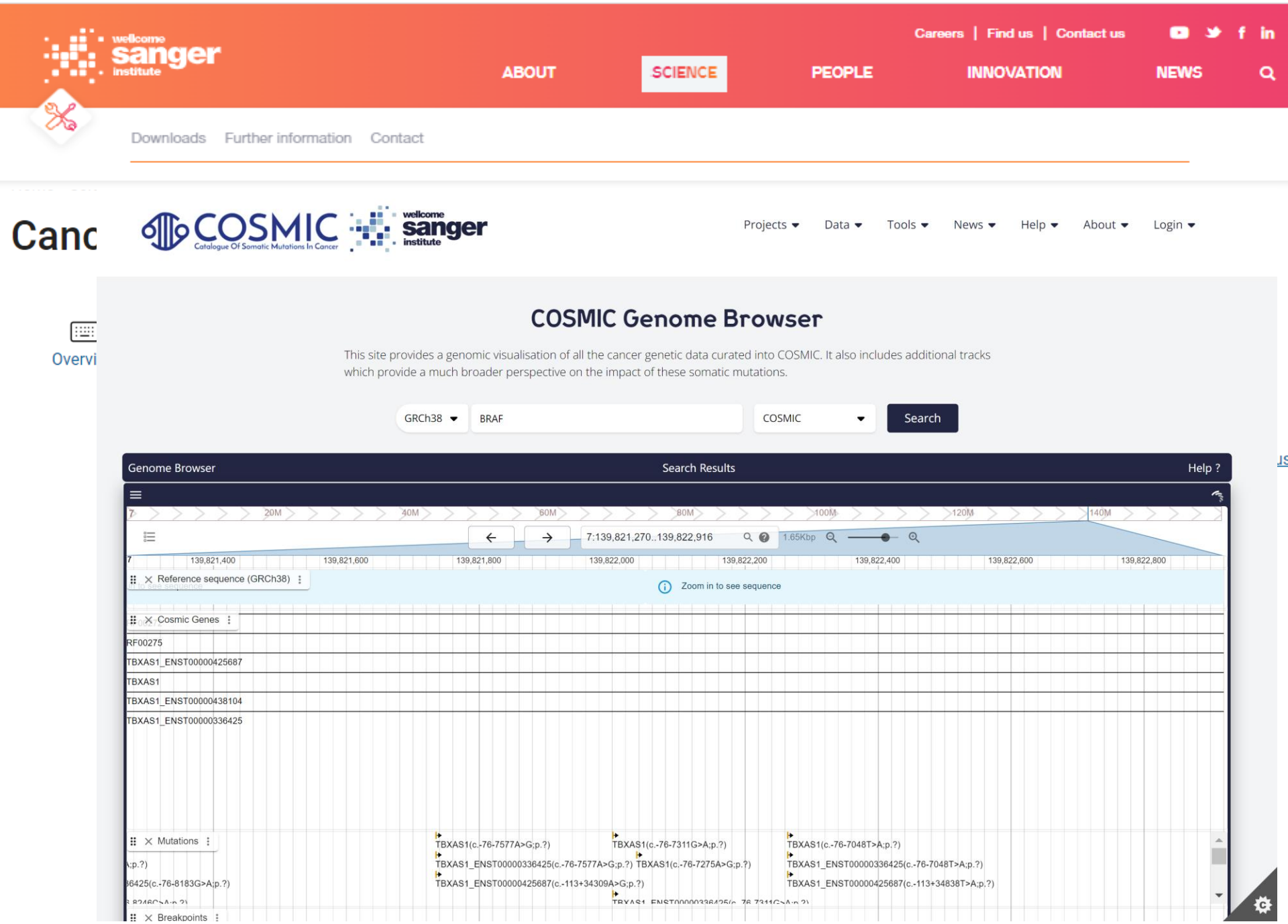
To celebrate the release of COSMIC v99, we delve into how focusing on expert manual curation of specific genes, resistance mutations & more emulates our dedication to being a reliable, sustainable source of genomic data on somatic mutations in cancer More...

Tools

- Cancer Browser — browse COSMIC data by tissue type and histology
- Genome Browser — browse the human genome with COSMIC annotations
- GA4GH Beacon — access COSMIC data through the GA4GH Beacon Project

Help

- Downloads — data that you can download from our SFTP site
- Documentation — view our help documentation
- FAQ — a compilation of our Frequently Asked Questions
- Release Notes — information about the latest COSMIC release
- Licensing — information about our licensing policy



https://cancer.sanger.ac.uk/cosmic/jbrowse/genome

Image credit: Marc Folland, Wellcome Sanger Institute

Innovation

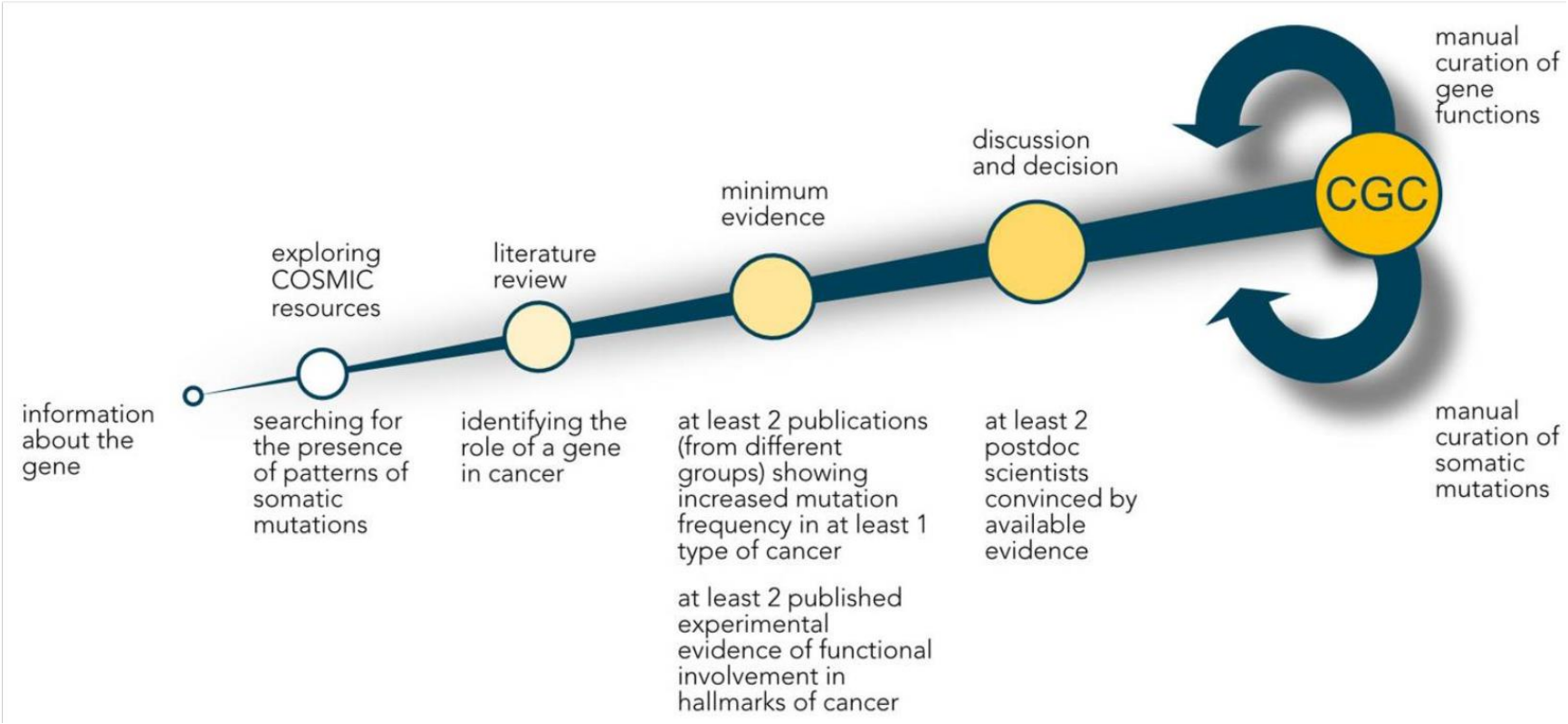
2 August 2024

Celebrating COSMIC and 20 years of enhancing cancer research

By Katrina Costa, Science Writer, Wellcome Sanger Institute

In 2024, COSMIC – the world's largest and most comprehensive resource on genetic mutations in cancer – celebrates two exciting milestones: COSMIC reaches its 20th anniversary and releases its 100th version of the database.

El Cancer Gene Census fué un esfuerzo en curso para catalogar los genes cuyas mutaciones han sido causalmente implicadas en cáncer. 748...

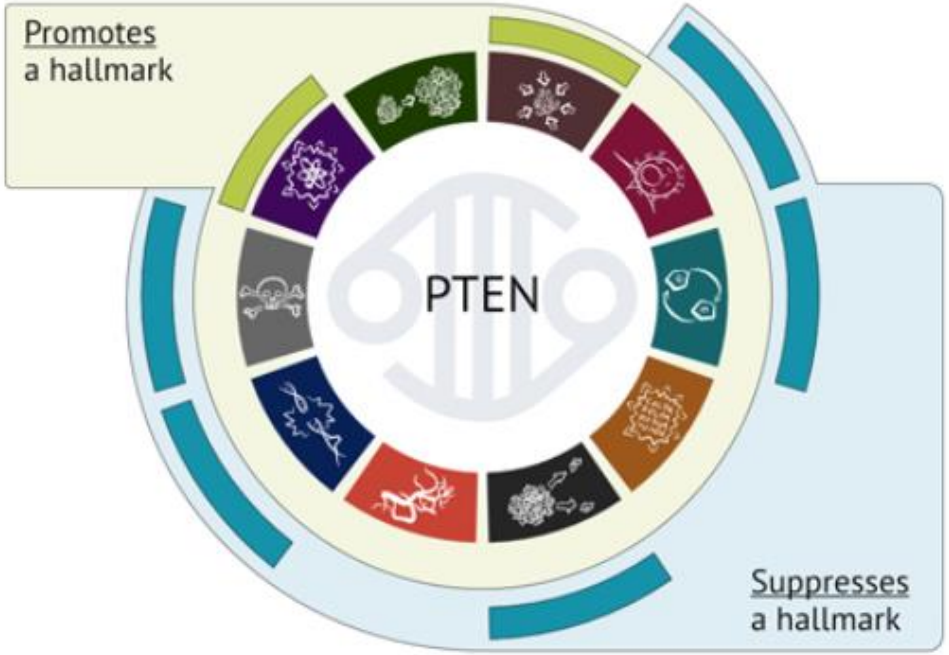


http://cancer.sanger.ac.uk/cancergenome/projects/census/

Nature Reviews Cancer volume 18, pages696–705 (2018)

The Cancer Gene Census

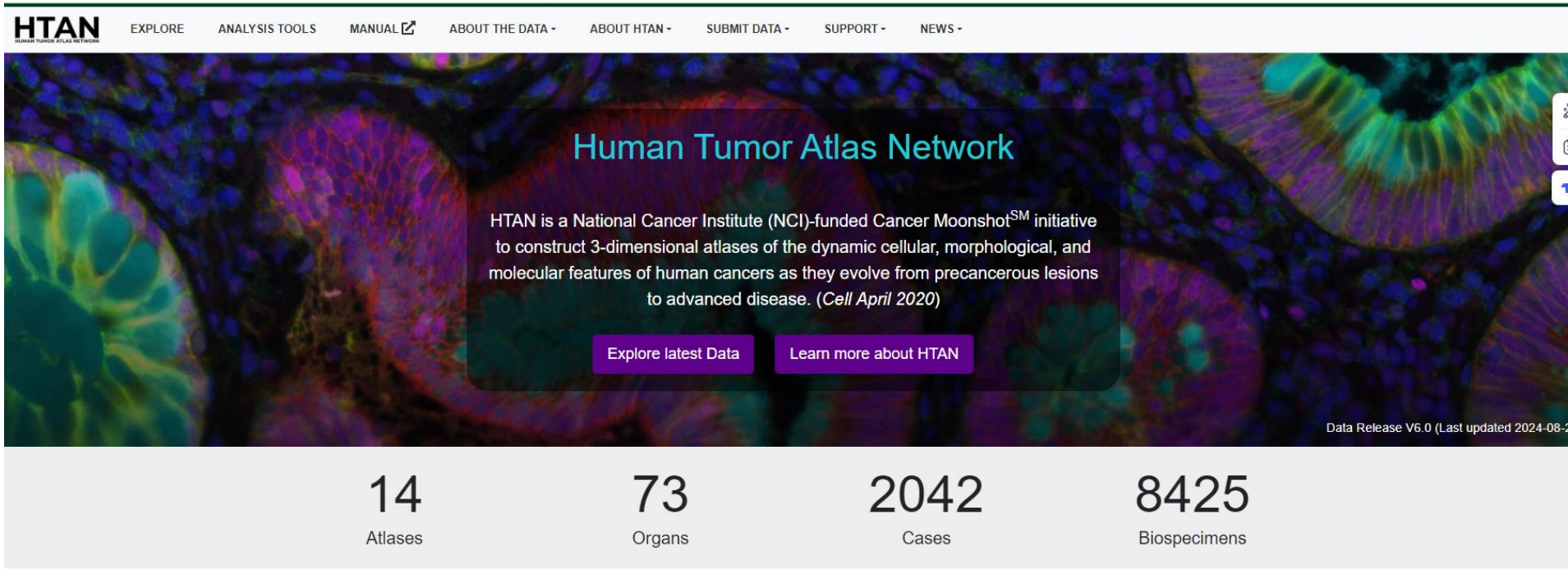
A.



B.

PTEN	P	S
Proliferative signalling		
Suppression of growth	■	
Escaping immune response to cancer		■
Cell replicative immortality		■
Tumour-promoting inflammation		
Invasion and metastasis		■
Angiogenesis		
Genome instability and mutations		■
Escaping programmed cell death		■
Change of cellular energetics	■	

Human Tumor Atlas Network



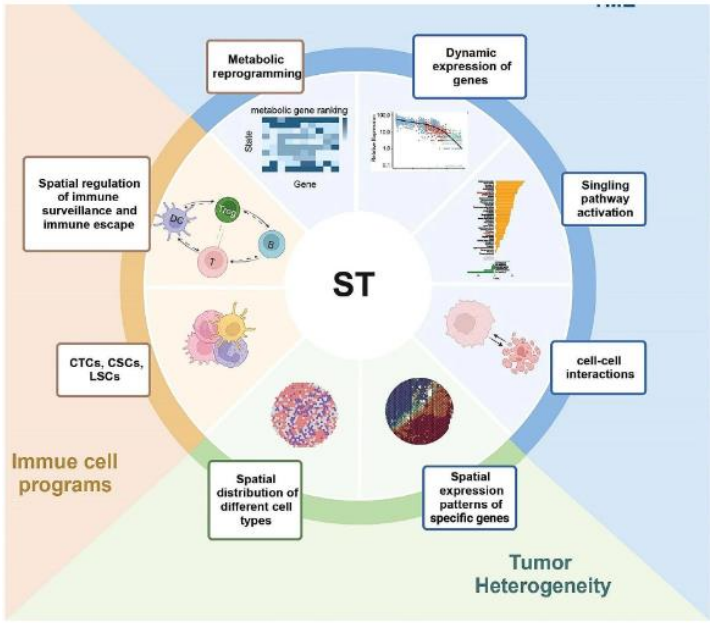
https://humantumoratlas.org/

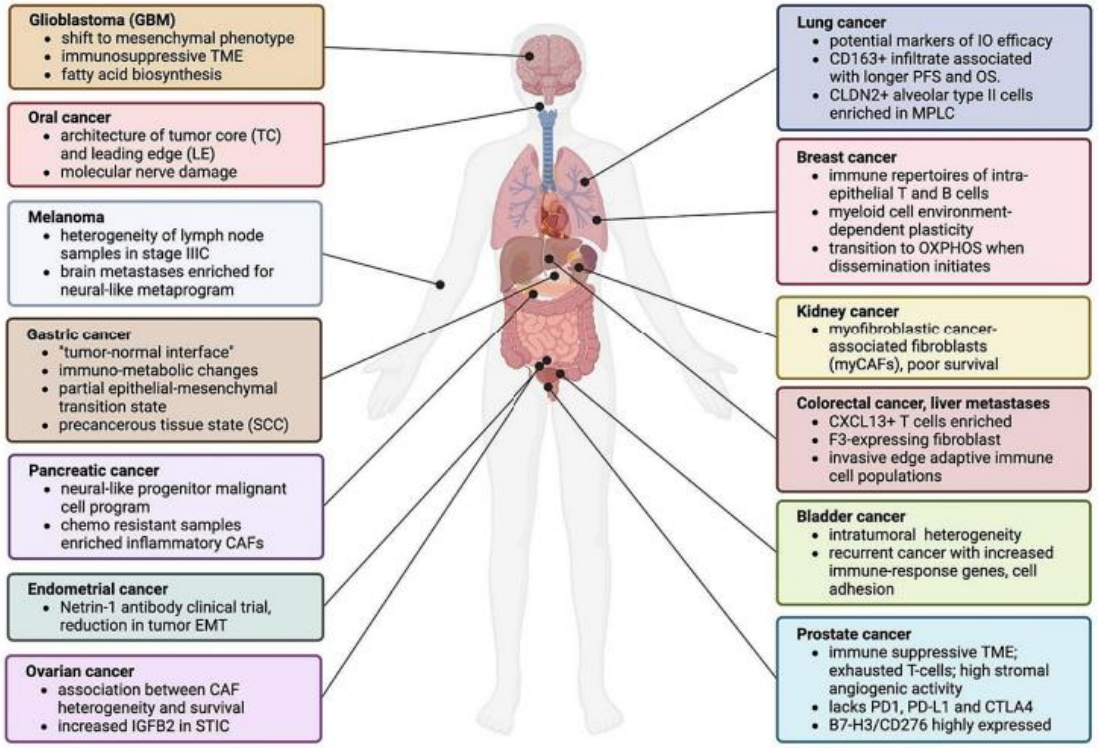
Transcriptómica Espacial

La transcriptómica espacial (ST) es el estudio y la cuantificación de transcripciones de ARN mensajero (ARNm) como sustituto de la expresión genética en el contexto espacial del cáncer y el microambiente asociado (Marx 2021; Moses y Pachter 2022).

Tecnologías representativas

- Laser capture microdissection-based approaches
- In situ imaging-based approaches
- Spatial indexing-based approaches





https://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-024-02040-9
https://link.springer.com/content/pdf/10.1007/s00432-024-05816-0.pdf

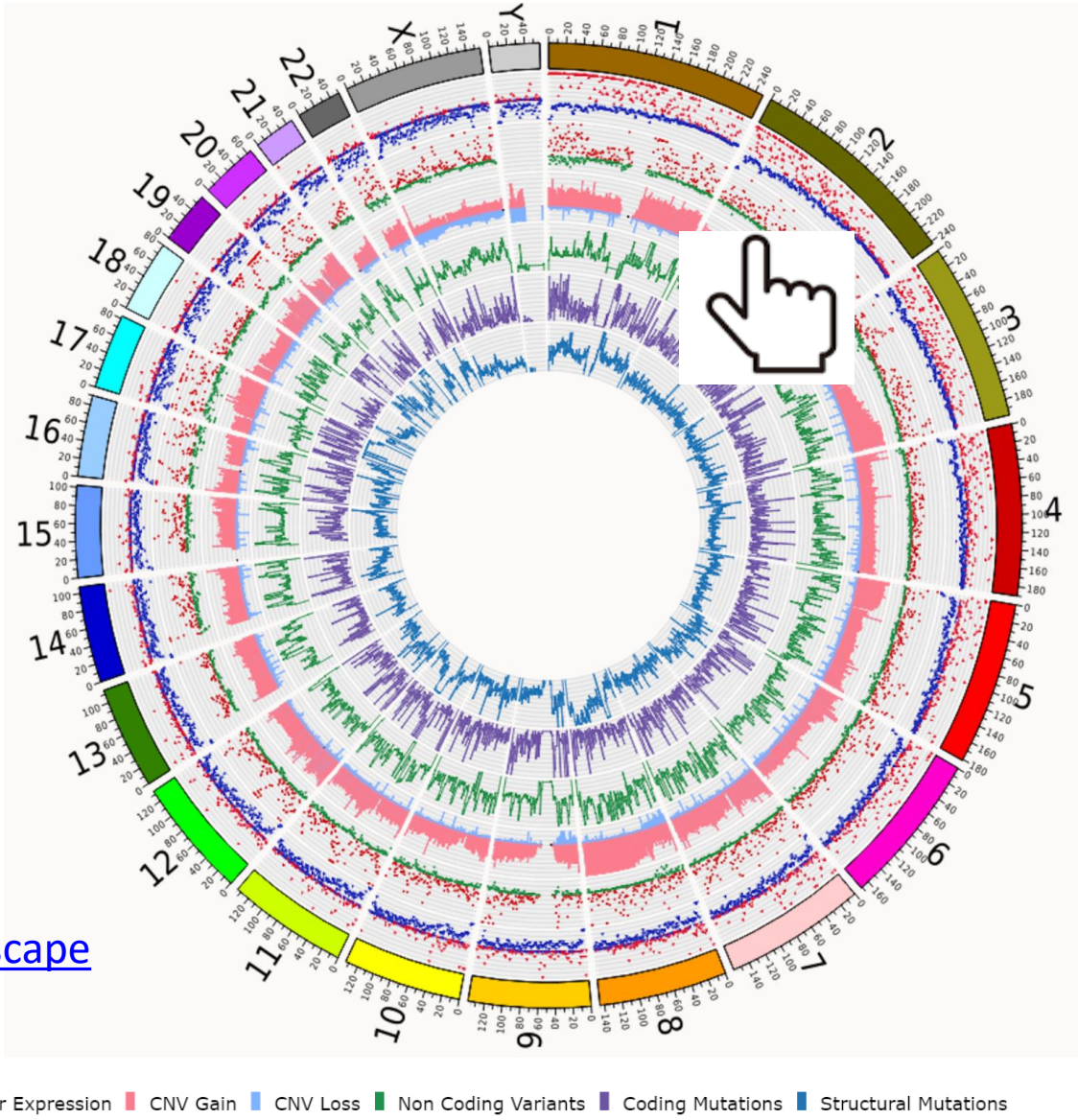
El genoma de todos los tumores conocidos

El cáncer es una enfermedad del genoma.

Heterogeneidad

Cambios especificos

Cambios pan-cancer



cBIOPORTAL

http://www.cbioportal.org/

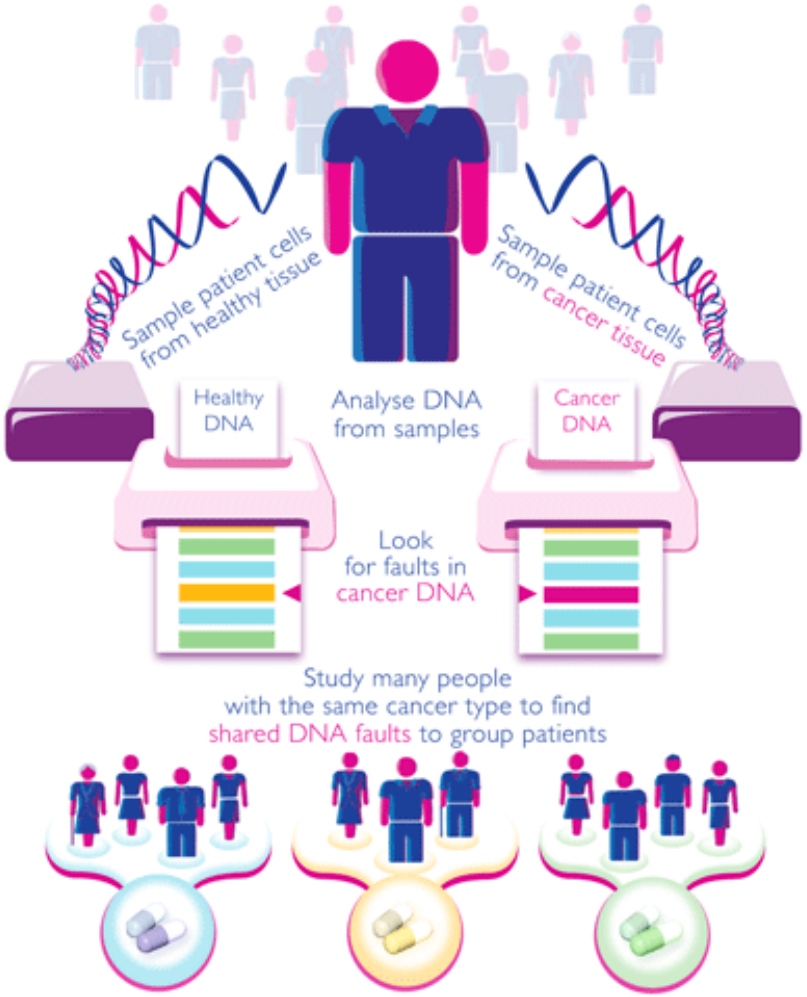
TCGA USA

COSMIC

http://cancer.sanger.ac.uk/cosmic/landscape

Sanger Institute UK

La importancia de conocer genomas normales



RESEARCH ARTICLE SUMMARY

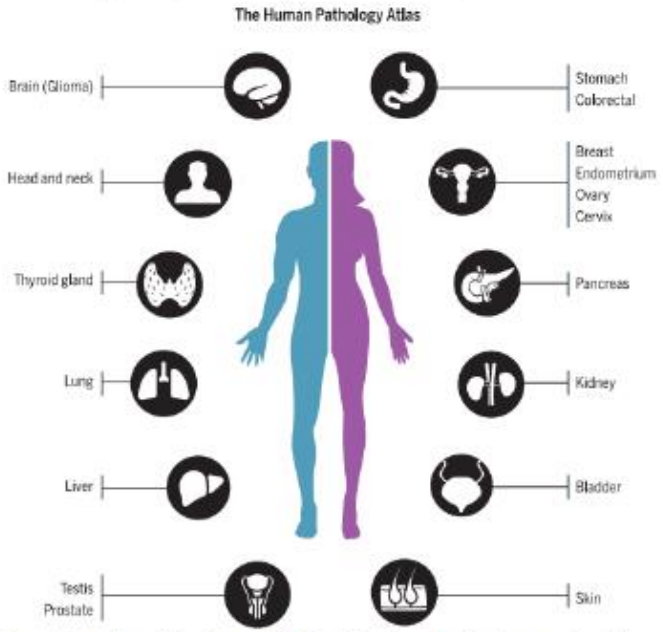
CANCER

A pathology atlas of the human cancer transcriptome

Mathias Uhlen,* Cheng Zhang, Sunjae Lee, Evelina Sjöstedt, Linn Fagerberg, Gholamreza Bidkhori, Rui Benfeitas, Muhammad Arif, Zhengtao Liu, Fredrik Edfors, Kemal Sanli, Kalle von Feilitzen, Per Oksvold, Emma Lundberg, Sophia Hober, Peter Nilsson, Johanna Mattsson, Jochen M. Schwenk, Hans Brunnström, Bengt Glimelius, Tobias Sjöblom, Per-Henrik Edqvist, Dijana Djureinovic, Patrick Micke, Cecilia Lindskog, Adil Mardinoglu,† Fredrik Ponten†

INTRODUCTION: Cancer is a leading cause of death worldwide, and there is great need to define the molecular mechanisms driving the development and progression of individual tumors. The Hallmarks of Cancer has provided a framework for a deeper molecular understanding of cancer, and the focus so far has been on the genetic alterations in individual cancers, including genome rearrangements, gene amplifications, and specific cancer-driving mutations. Using systems-level approaches, it is now also possible to define downstream effects of individual genetic alterations in a genome-wide manner.

RATIONALE: In our study, we used a systems-level approach to analyze the transcriptome of 17 major cancer types with respect to clinical outcome, based on a genome-wide transcriptomics analysis of ~8000 individual patients with clinical metadata. The study was made possible through the availability of large open-access knowledge-based efforts such as the Cancer Genome Atlas and the Human Protein Atlas. Here, we used the data to perform a systems-level analysis of 17 major human cancer types, describing both interindividual and intertumor variation patterns.



Schematic overview of the Human Pathology Atlas. A systems-level approach enables analysis of the protein-coding genes of 17 different cancer types from ~8000 patients. Results are available in an interactive open-access database.

RESULTS: The analysis identified candidate prognostic genes associated with clinical outcome for each tumor type; the results show that a large fraction of cancer protein-coding genes are differentially expressed and, in many cases, have an impact on overall patient survival. Systems biology analyses revealed that gene expression of individual tumors within a particular cancer varied considerably and could exceed the variation observed between distinct cancer types. No general prognostic gene necessary for clinical outcome was applicable to all cancers. Shorter patient survival was generally associated with up-regulation of genes involved in mitosis and cell growth and down-regulation of genes involved in cellular differentiation. The data allowed us to generate personalized genome-scale metabolic models for cancer patients to identify key genes involved in tumor growth. In addition, we explored tissue-specific genes associated with the dedifferentiation of tumor cells and the role of specific cancer testis antigens on a genome-wide scale. For lung and colorectal cancer, a selection of prognostic genes identified by the systems biology effort were analyzed in independent, prospective cancer cohorts using immunohistochemistry to validate the gene expression patterns at the protein level.

ON OUR WEBSITE

Read the full article at http://dx.doi.org/10.1126/science.aan2507

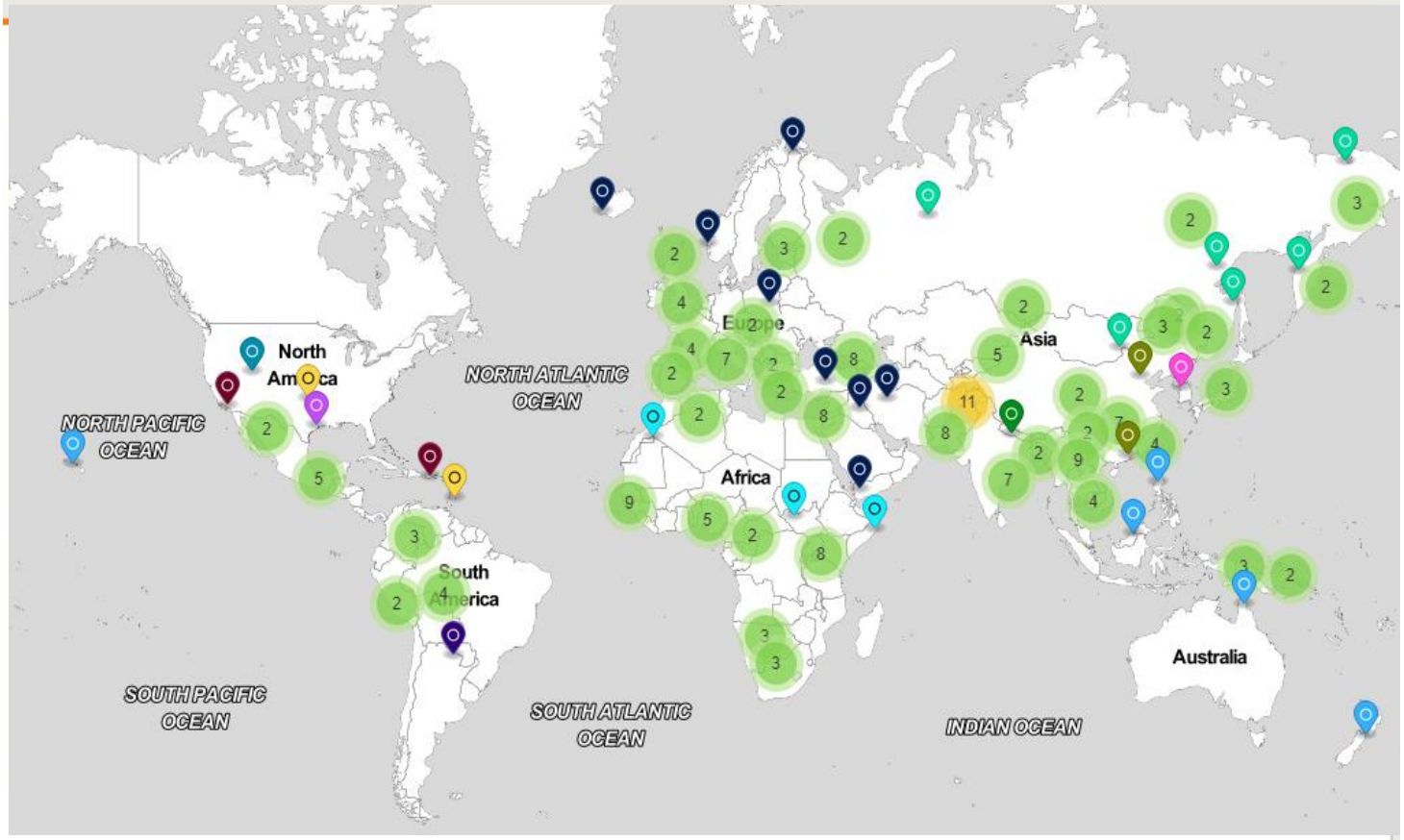
CONCLUSION: A Human Pathology Atlas has been created as part of the Human Protein Atlas program to explore the prognostic role of each protein-coding gene in 17 different cancers. Our atlas uses transcriptomics and antibody-based profiling to provide a standalone resource for cancer precision medicine. The results demonstrate the power of large systems biology efforts that make use of publicly available resources. Using genome-scale metabolic models, cancer patients are shown to have widespread metabolic heterogeneity, highlighting the need for precise and personalized medicine for cancer treatment. With more than 900,000 Kaplan-Meier plots, this resource allows exploration of the specific genes influencing clinical outcome for major cancers, paving the way for further in-depth studies incorporating systems-level analyses of cancer. All data presented are available in an interactive open-access database (www.proteinatlas.org/pathology) to allow for genome-wide exploration of the impact of individual proteins on clinical outcome in major human cancers. ■

The list of author affiliations is available in the full article online.
*Corresponding author. Email: mathias.uhlen@scilifelab.se
†These authors contributed equally to this work.
Cite this article as M. Uhlen et al., Science 357, eaan2507 (2017). DOI: 10.1126/science.aan2507

IGSR: The International Genome Sample Resource

Providing ongoing support for the 1000 Genomes Project data

Home About Data Portal Analysis Contact Browser FAQ



The International Genome Sample Resource (IGSR) was established to ensure the ongoing usability of data generated by the 1000 Genomes Project and to extend the data set. More information is available about the IGSR.

www.internationalgenome.org

African Ancestry
American Ancestry
Africa (HGDP)
America (HGDP)
Middle East (HGDP)
Oceania (HGDP)
East Asia (SGDP)
Oceania (SGDP)
East Asian Ancestry
European Ancestry
Central South Asia (HGDP)
East Asia (HGDP)
Africa (SGDP)
America (SGDP)
South Asia (SGDP)
West Eurasia (SGDP)
South Asian Ancestry
Europe (HGDP)
Central Asia and Siberia (SGDP)

A global reference for human genetic variation *Nature 526, 68–74 (01 October 2015)*
An integrated map of structural variation in 2,504 human genomes *Nature 526, 75–81 (01 October 2015)*

ExAC is acronym for:

Exome
Aggregation
Consortium

Not all 'healthy' individuals

gnomAD

Genome
Aggregation
Database

123,136 exome sequences and
15,496 whole-genome sequences

http://gnomad.broadinstitute.org/

ARTICLE

OPEN

doi:10.1038/nature19057

Analysis of protein-coding genetic variation in 60,706 humans

Monkol Lek[1,2,3,4], Konrad J. Karczewski[1,2*], Eric V. Minikel[1,2,5*], Kaitlin E. Samocha[1,2,5,6*], Eric Banks[2], Timothy Fennell[2], Anne H. O'Donnell-Luria[1,2,7], James S. Ware[2,8,9,10,11], Andrew J. Hill[1,2,12], Beryl B. Cummings[1,2,5], Taru Tukiainen[1,2], Daniel P. Birnbaum[2], Jack A. Kosmicki[1,2,6,13], Laramie E. Duncan[1,2,6], Karol Estrada[1,2], Fengmei Zhao[1,2], James Zou[2], Emma Pierce-Hoffman[1,2], Joanne Berghout[14,15], David N. Cooper[16], Nicole Deflaux[17], Mark DePristo[18], Ron Do[19,20,21,22], Jason Flannick[2,23], Menachem Fromer[1,6,19,20,24], Laura Gauthier[18], Jackie Goldstein[1,2,6], Namrata Gupta[2], Daniel Howrigan[1,2,6], Adam Kiezun[18], Mitja I. Kurki[2,25], Ami Levy Moonshine[18], Pradeep Natarajan[2,26,27,28], Lorena Orozco[29], Gina M. Peloso[2,27,28], Ryan Poplin[18], Manuel A. Rivas[2], Valentin Ruano-Rubio[18], Samuel A. Rose[6], Douglas M. Ruderfer[19,20,24], Khalid Shakir[18], Peter D. Stenson[16], Christine Stevens[2], Brett P. Thomas[1,2], Grace Tiao[18], Maria T. Tusie-Luna[30], Ben Weisburd[2], Hong-Hee Won[31], Dongmei Yu[6,25,27,32], David M. Altshuler[2,33], Diego Ardissino[34], Michael Boehnke[35], John Danesh[36], Stacey Donnelly[2], Roberto Elosua[37], Jose C. Florez[2,26,27], Stacey B. Gabriel[2], Gad Getz[18,26,38], Stephen J. Glatt[39,40,41], Christina M. Hultman[42], Sekar Kathiresan[2,26,27,28], Markku Laakso[43], Steven McCarroll[6,8], Mark I. McCarthy[44,45,46], Dermot McGovern[47], Ruth McPherson[48], Benjamin M. Neale[1,2,6], Aarno Palotie[1,2,5,49], Shaun M. Purcell[19,20,24], Danish Saleheen[50,51,52], Jeremiah M. Scharf[2,6,25,27,32], Pamela Sklar[19,20,24,53,54], Patrick F. Sullivan[55,56], Jaakko Tuomilehto[57], Ming T. Tsuang[58], Hugh C. Watkins[44,59], James G. Wilson[60], Mark J. Daly[1,2,6], Daniel G. MacArthur[1,2] & Exome Aggregation Consortium†

Large-scale reference data sets of human genetic variation are critical for the medical and functional interpretation of DNA sequence changes. Here we describe the aggregation and analysis of high-quality exome (protein-coding region) DNA sequence data for 60,706 individuals of diverse ancestries generated as part of the Exome Aggregation Consortium (ExAC). This catalogue of human genetic diversity contains an average of one variant every eight bases of the exome, and provides direct evidence for the presence of widespread mutational recurrence. We have used this catalogue to calculate objective metrics of pathogenicity for sequence variants, and to identify genes subject to strong selection against various classes of mutation; identifying 3,230 genes with near-complete depletion of predicted protein-truncating variants, with 72% of these genes having no currently established human disease phenotype. Finally, we demonstrate that these data can be used for the efficient filtering of candidate disease-causing variants, and for the discovery of human 'knockout' variants in protein-coding genes.

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[10]NIHR Royal Brompton Cardiovascular Biomedical Research Unit, Royal Brompton Hospital, London SW3 6NP, UK. [11]MRC Clinical Sciences Centre, Imperial College London, London SW7 2AZ, UK. [12]Genome Sciences, University of Washington, Seattle, Washington 98195, USA. [13]Program in Bioinformatics and Integrative Genomics, Harvard Medical School, Boston, Massachusetts 02115, USA. [14]Mouse Genome Informatics, Jackson Laboratory, Bar Harbor, Maine 04609, USA. [15]Center for Biomedical Informatics and Biostatistics, University of Arizona, Tucson, Arizona 85721, USA. [16]Institute of Medical Genetics, Cardiff University, Cardiff CF10 3XQ, UK. [17]Google, Mountain View, California 94043, USA. [18]Broad Institute of MIT and Harvard, Cambridge, Massachusetts 02142, USA. [19]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. [20]Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. [21]The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. [22]The Center for Statistical Genetics, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. [23]Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. [24]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. [25]Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. [26]Harvard Medical School, Boston, Massachusetts 02115, USA. [27]Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. [28]Cardiovascular Research Center, Massachusetts General Hospital, Boston, Massachusetts 02114, USA. 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[38]Department of Pathology and Cancer Center, Massachusetts General Hospital, Boston, Massachusetts, 02114 USA. [39]Psychiatric Genetic Epidemiology & Neurobiology Laboratory, State University of New York, Upstate Medical University, Syracuse, New York 13210, USA. [40]Department of Psychiatry and Behavioral Sciences, State University of New York, Upstate Medical University, Syracuse, New York 13210, USA. [41]Department of Neuroscience and Physiology, State University of New York, Upstate Medical University, Syracuse, New York 13210, USA. [42]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, SE-171 77 Stockholm, Sweden. [43]Department of Medicine, University of Eastern Finland and Kuopio University Hospital, 70211 Kuopio, Finland. [44]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX1 2JD, UK. [45]Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford OX1 2JD, UK. [46]Oxford NIHR Biomedical Research Centre, Oxford University Hospitals Foundation Trust, Oxford OX1 2JD, UK. [47]Inflammatory Bowel Disease and Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles, California 90048, USA. [48]Atherogenomics Laboratory, University of Ottawa Heart Institute, Ottawa, Ontario K1Y 4W7, Canada. [49]Institute for Molecular Medicine Finland (FIMM), University of Helsinki, 00100 Helsinki, Finland. [50]Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA. [51]Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA. [52]Center for Non-Communicable Diseases, Karachi, Pakistan. [53]Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. [54]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. [55]Department of Genetics, University of North Carolina, Chapel Hill, North Carolina 27599, USA. [56]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet SE-171 77 Stockholm, Sweden. [57]Department of Public Health, University of Helsinki, 00100 Helsinki, Finland. [58]Department of Psychiatry, University of California, San Diego, California 92093, USA. [59]Radcliffe Department of Medicine, University of Oxford, Oxford OX1 2JD, UK. [60]Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi 39216, USA.
†A list of participants and their affiliations appears in the Supplementary Information.
*These authors contributed equally to this work.

gnomAD v3 released! 71,702 genomes aligned on GRCh38.

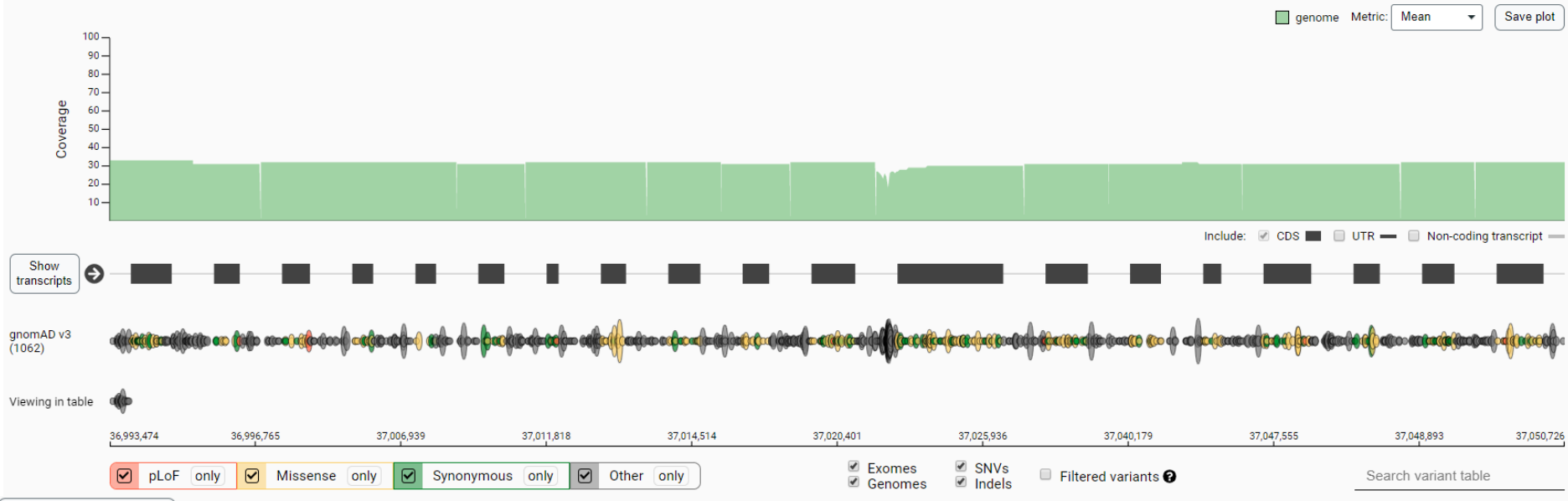
MLH1 mutL homolog 1

Dataset: gnomAD v3 | gnomAD SVs v2.1

Genome build GRCh38 / hg38
Ensembl gene ID ENSG00000076242
Canonical transcript ID ENST00000231790
Region 3:36993333-37050919
References Ensembl, UCSC Browser, and more

Constraint

Constraint not yet available for gnomAD v3.



pLoF only | Missense only | Synonymous only | Other only

Exomes | Genomes | SNVs | Indels | Filtered variants

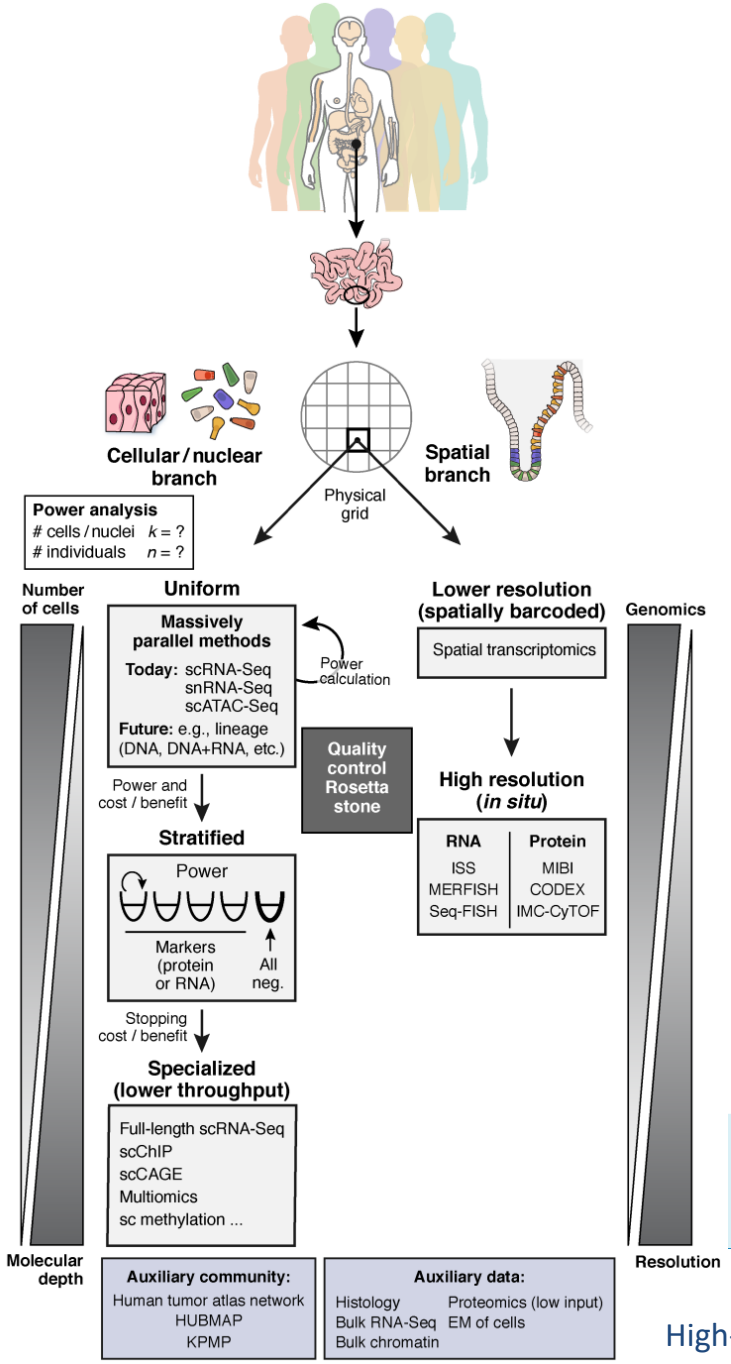
Search variant table

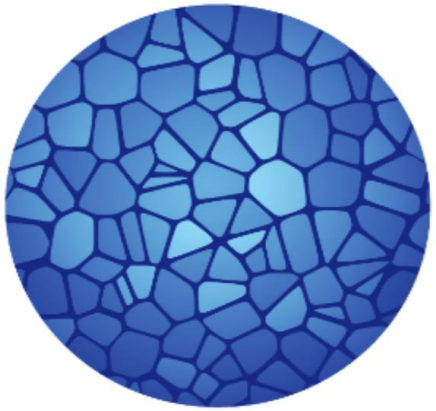
Export variants to CSV

Only variants located in or within 75 base pairs of a coding exon are shown here. To see intronic variants, use the region view.

† denotes a consequence that is for a non-canonical transcript

Variant ID	Source	Consequence	Annotation	Flags	Allele Count	Allele Number	Allele Frequency	Number of Homozygotes
3-36993485-G-A	G	c.-63G>A	5' UTR		1	143374	6.97e-6	0
3-36993500-C-T	G	c.-48C>T	5' UTR		4	143360	2.79e-5	0
3-36993501-A-C	G	c.-47A>C	5' UTR		1	143376	6.97e-6	0
3-36993503-T-G	G	c.-45T>G	5' UTR		1	143368	6.98e-6	0
3-36993504-T-C	G	c.-44T>C	5' UTR		1	143338	6.98e-6	0
3-36993504-T-G	G	c.-44T>G	5' UTR		1	143338	6.98e-6	0
3-36993505-C-T	G	c.-43C>T	5' UTR		2	143358	1.4e-5	0
3-36993506-C-T	G	c.-42C>T	5' UTR		13	143350	9.07e-5	0
3-36993511-A-G	G	c.-37A>G	5' UTR		1	143356	6.98e-6	0





'HE HUMAN CELL ATLAS

White Paper

The HCA Consortium

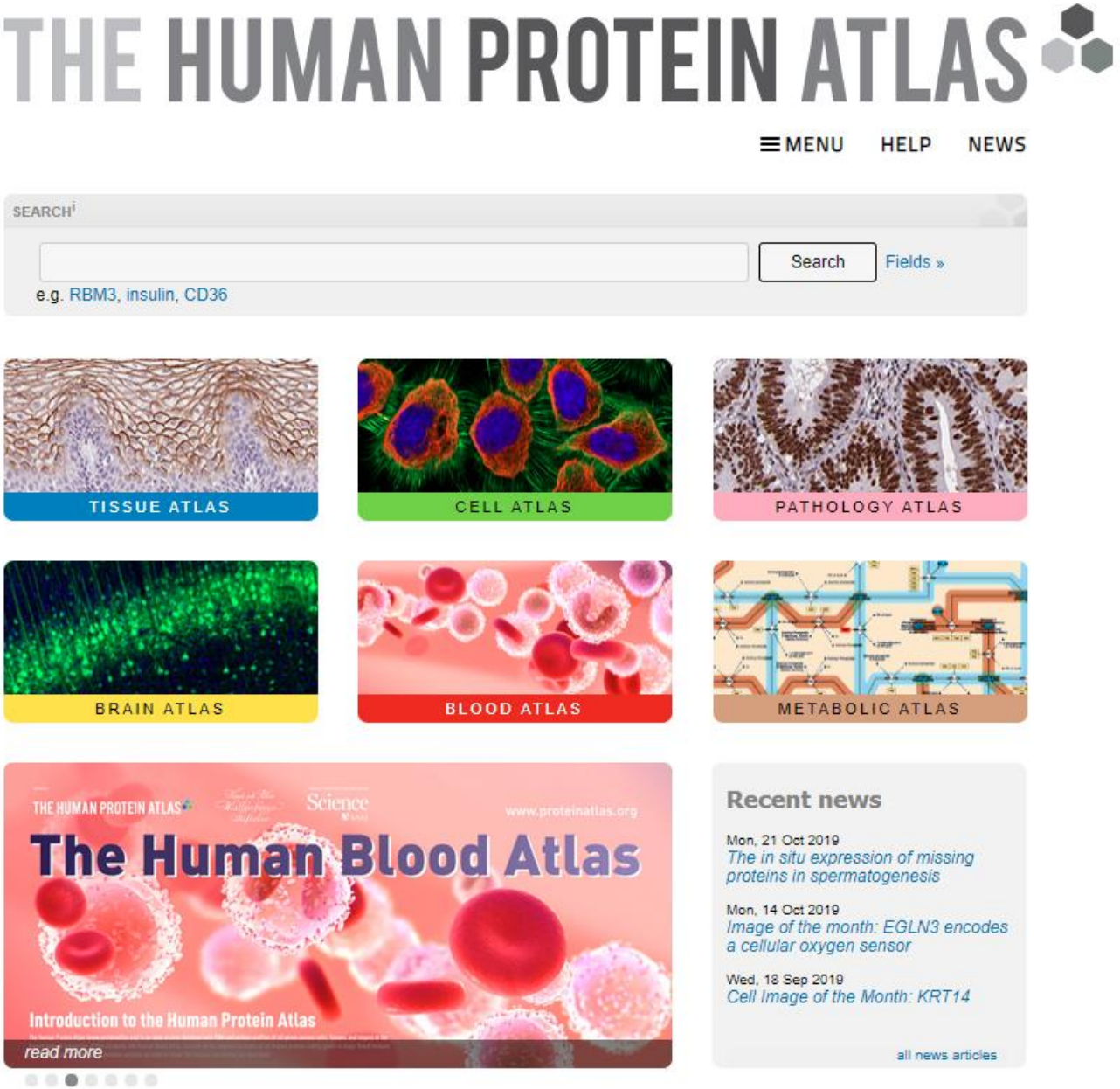
October 18, 2017

Comprehensive reference maps of all human cells
comprehensive reference maps of all human cells:

30 million to 100 million
cells (1st draft)

30.6M CELLS | 4.5k DONORS | 288 PROJECTS | 468 LABS

High-resolution analysis of large tissues in two (2-D) or three (3-D) dimensions
Single-cell transcriptome



https://www.proteinatlas.org/

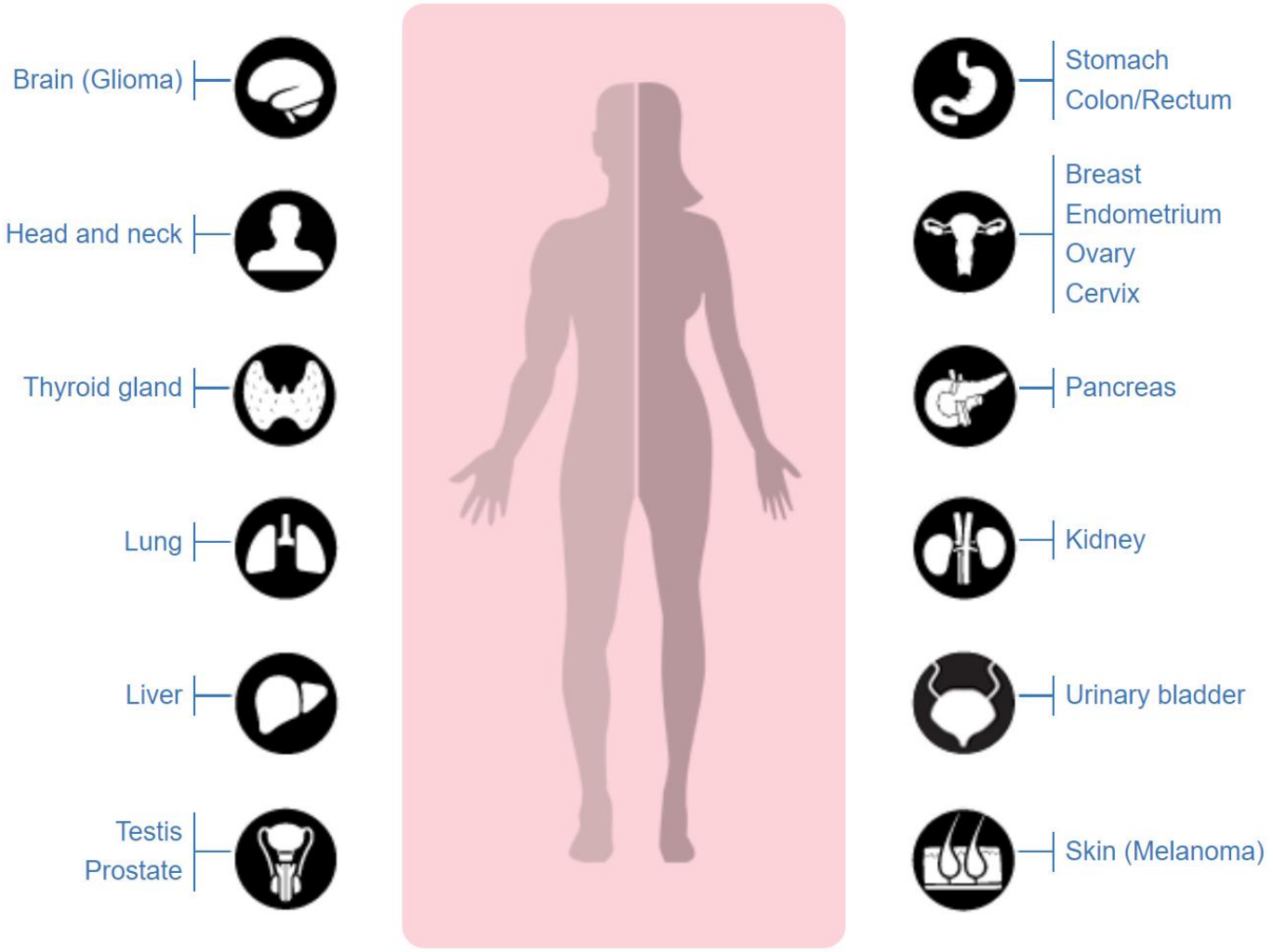
THE HUMAN PROTEIN ATLAS

SECTIONS ABOUT NEWS LEARN DATA HELP

SECTI

THE CANCER PROTEOMES[i]

Interactive chapters regarding each of the 17 cancer types explore mRNA and protein expression data, including genes associated with prognosis.



17 major cancer

8000 individual p
with clinical meta

Survival analysis
More than 100 m
Kaplan-Meier plc

www.proteinatlas.


Coffee
Break

Genómica de cáncer

- Concepto biológico de Cáncer
- Los genes de cáncer y sus mutaciones
- El genoma del cáncer: mutaciones
- El proyecto genoma de cáncer
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P3-Las mutaciones de una célula tumoral de mama

- Son iguales en todos las células de ese tumor del mismo paciente?
- Son iguales entre tumores distintos del mismo paciente?
- Son iguales en pacientes diferentes?
- Son diferentes a las de otro tipo de tumor (ej: pulmón, hígado):
  - Tipo de genes
  - Tipo de mutación
  - Número

http://www.hhmi.org/biointeractive/interview-dr-bert-vogelstein

CANCERGENOMICS
www.sciencemag.org/special/cancergenomics

Pathways that control colorectal tumorigenesis...

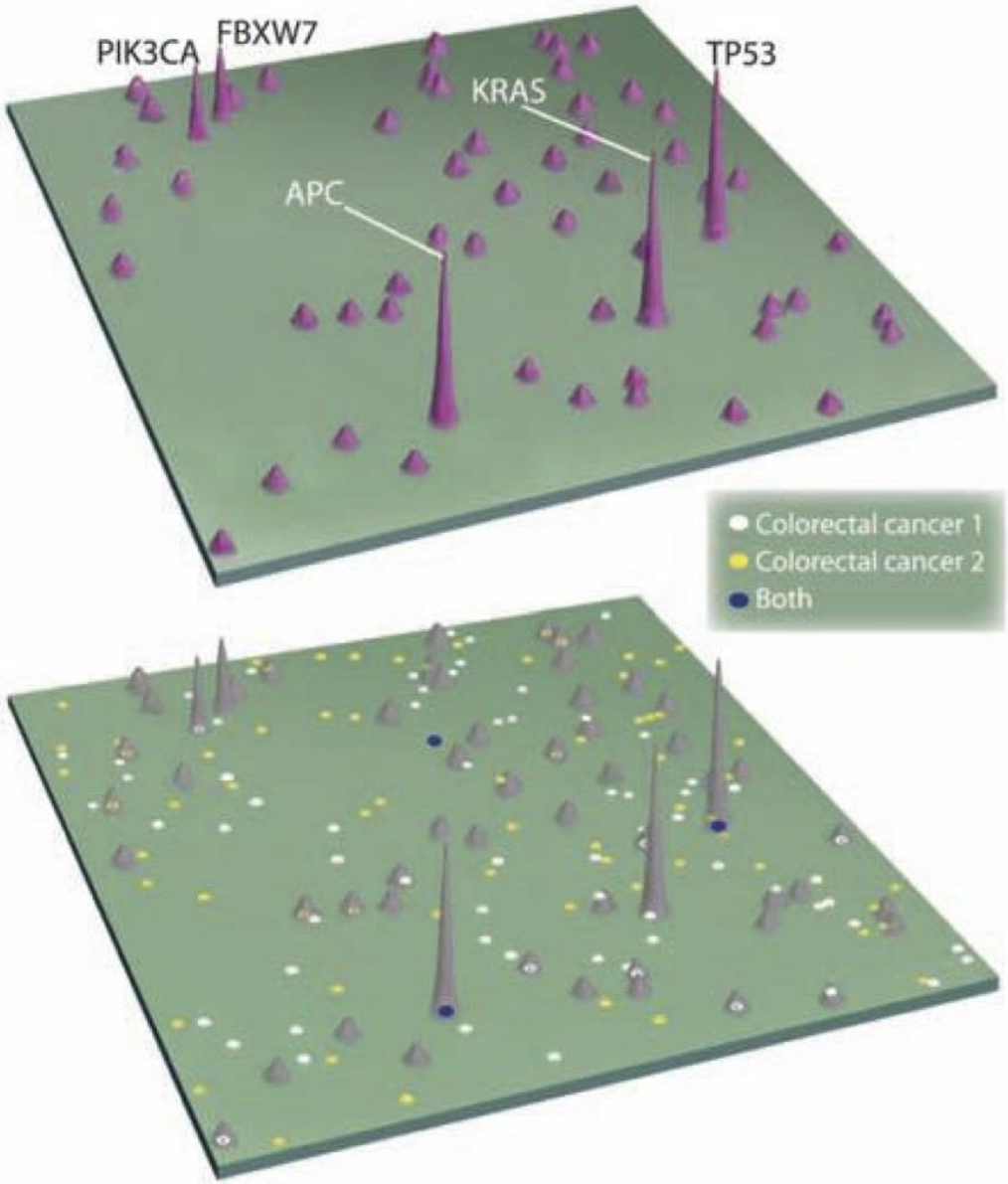
REVIEW

Cancer Genome Landscapes

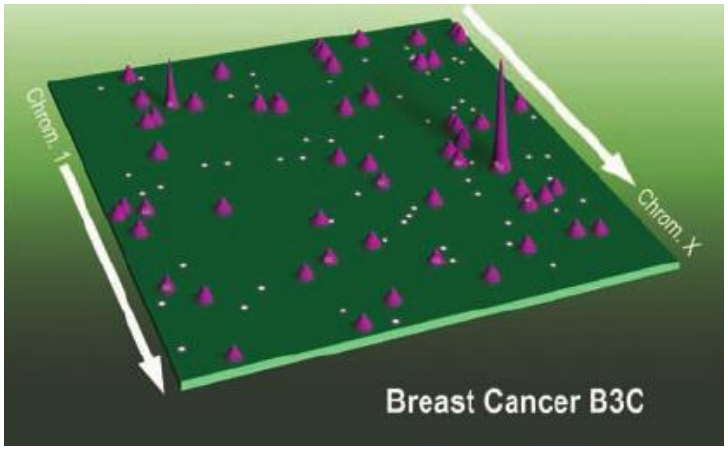
Bert Vogelstein, Nickolas Papadopoulos, Victor E. Velculescu, Shibin Zhou,
Luis A. Diaz Jr., Kenneth W. Kinzler*

Over the past decade, comprehensive sequencing efforts have revealed the genomic landscapes of common forms of human cancer. For most cancer types, this landscape consists of a small number of "mountains" (genes altered in a high percentage of tumors) and a much larger number of "hills" (genes altered infrequently). To date, these studies have revealed ~140 genes that, when altered by intragenic mutations, can promote or "drive" tumorigenesis. A typical tumor contains two to eight of these "driver gene" mutations; the remaining mutations are passengers that confer no selective growth advantage. Driver genes can be classified into 12 signaling pathways that regulate three core cellular processes: cell fate, cell survival, and genome maintenance. A better understanding of these pathways is one of the most pressing needs in basic cancer research. Even now, however, our knowledge of cancer genomes is sufficient to guide the development of more effective approaches for reducing cancer morbidity and mortality.

Genomic Landscape of Colorectal Cancer

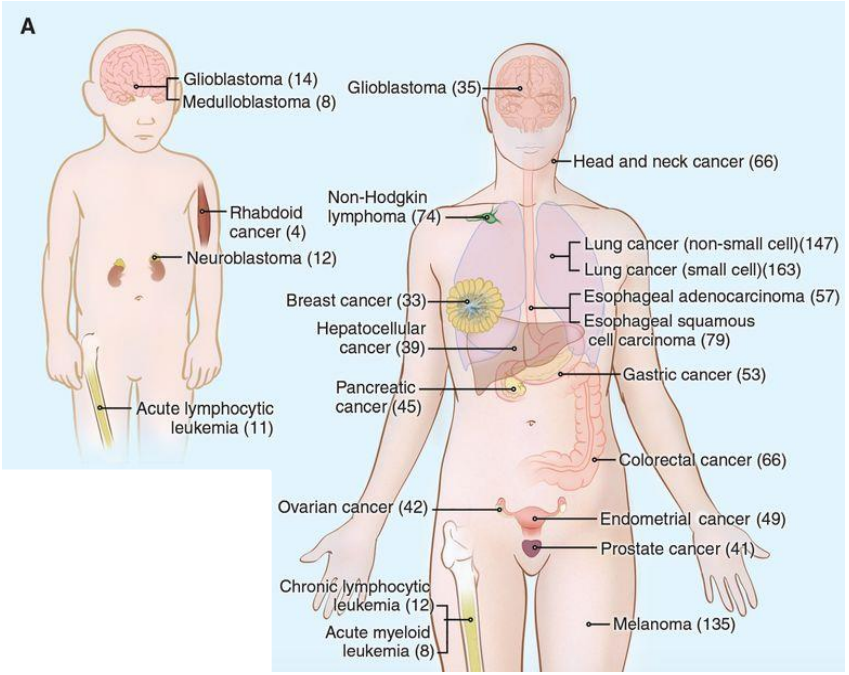


A two-dimensional map of genes mutated in colorectal cancers, in which a few gene "mountains" are mutated in a large proportion of tumors while most "hills" are mutated infrequently. The mutations in two individual tumors are indicated on the lower map.

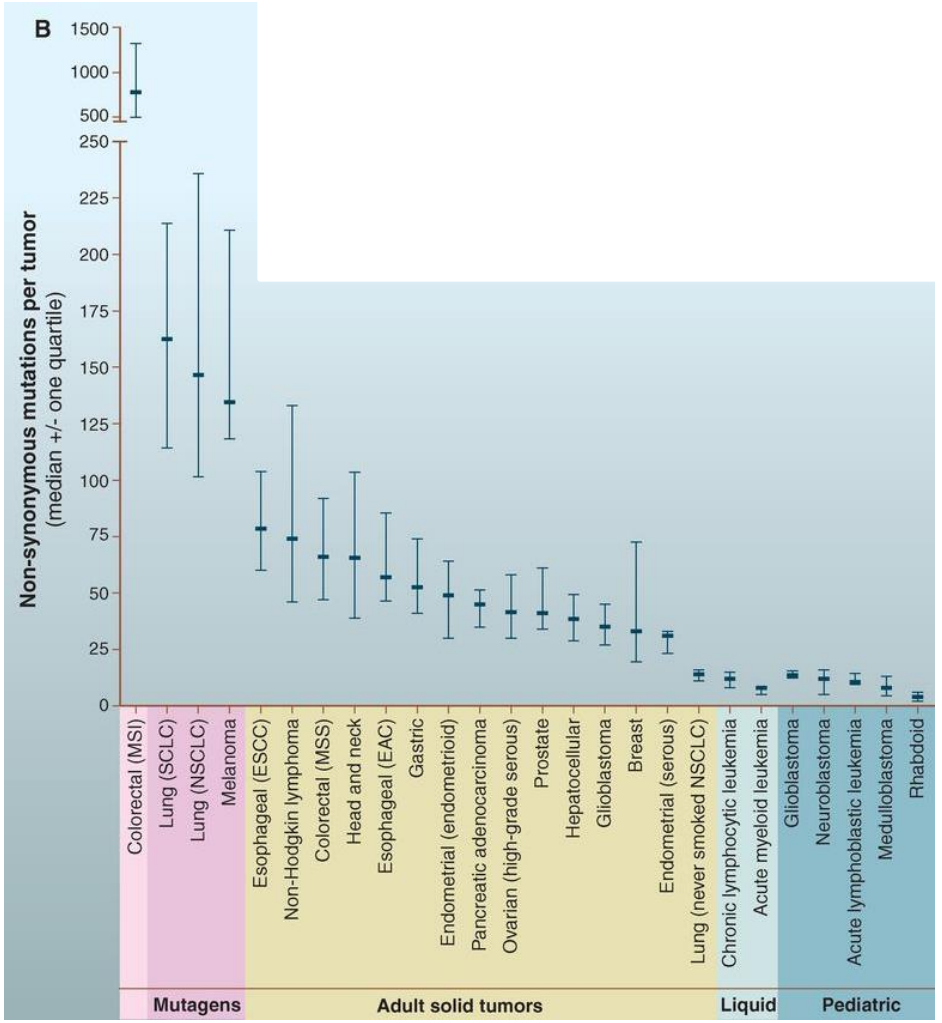


Wood, L and B. Vogelstein, Science Vol. 318, November, 2007

Fig. 1 Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies.



Number of nonsynonymous mutations per tumor.

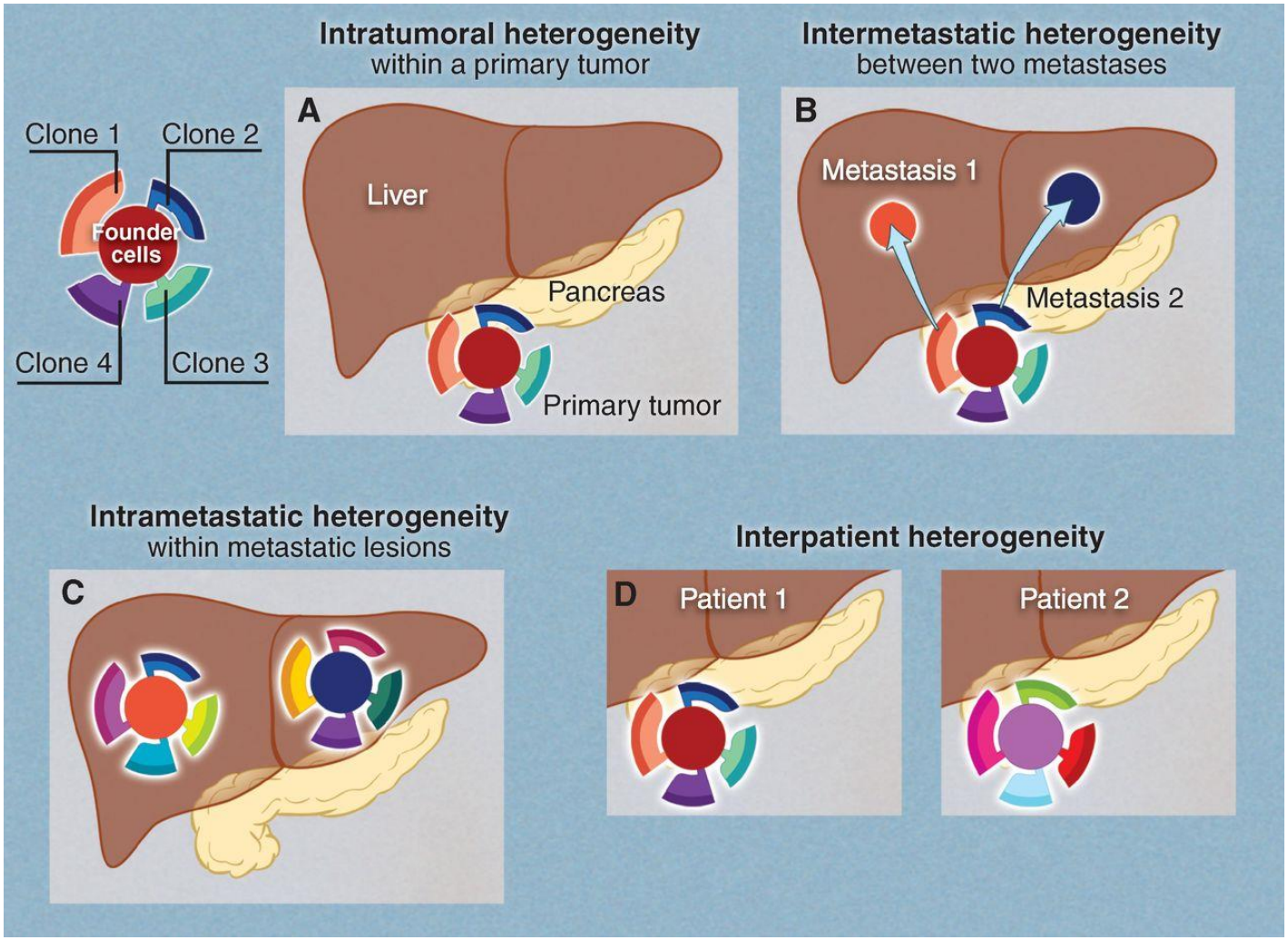


Mutagens in the pathogenesis
Defects in DNA repair

Published by AAAS

B Vogelstein et al. Science 2013;339:1546-1558

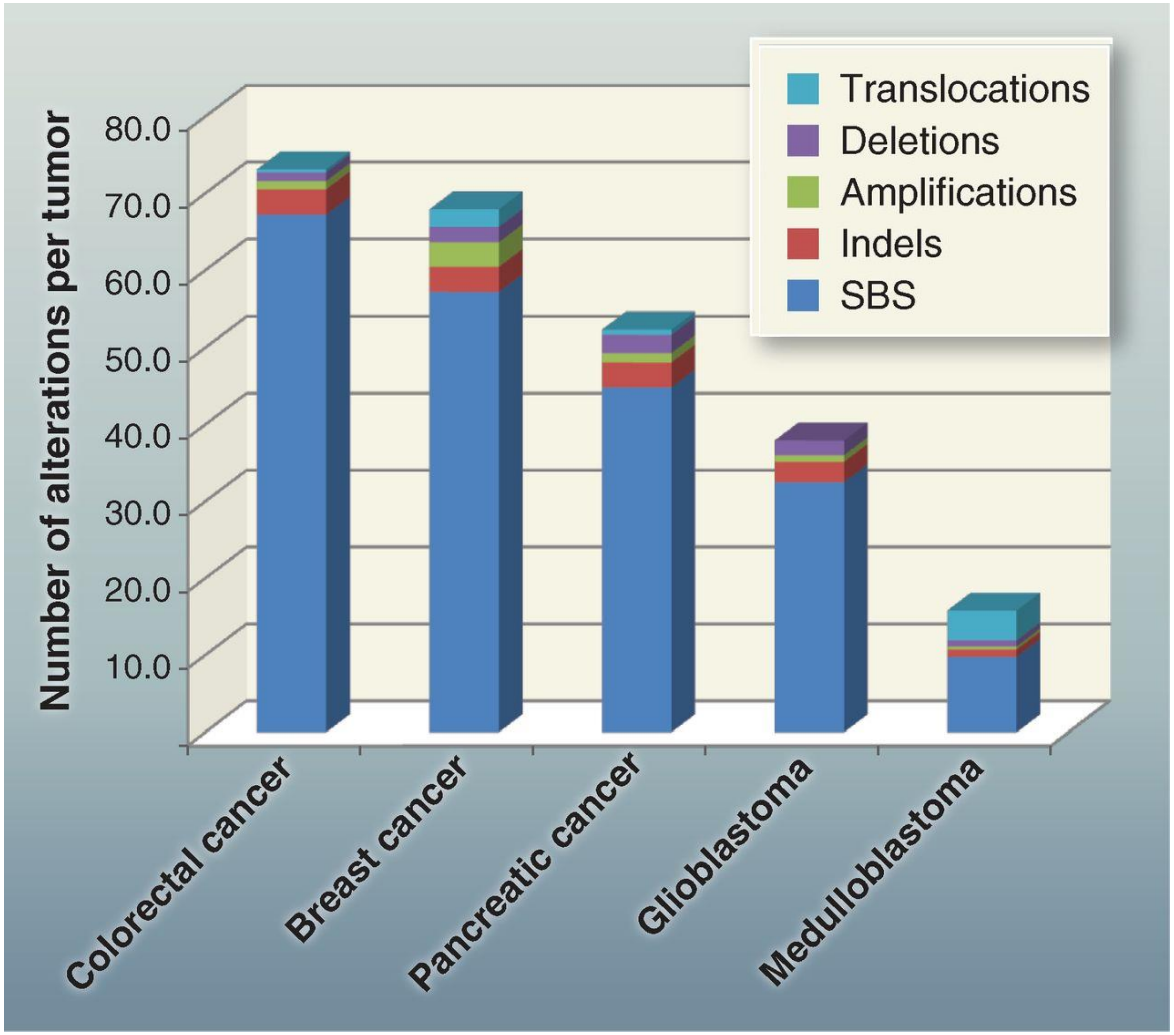
Fig. 6 Four types of genetic heterogeneity in tumors, illustrated by a primary tumor in the pancreas and its metastatic lesions in the liver.



B Vogelstein et al. Science 2013;339:1546-1558

Fig. 3 Total alterations affecting protein-coding genes in selected tumors.

Total alterations affecting protein-coding genes in selected tumors. Average number and types of genomic alterations per tumor, including single-base substitutions (SBS), small insertions and deletions (indels), amplifications, and homozygous deletions, as determined by genome-wide sequencing studies. For colorectal, breast, and pancreatic ductal cancer, and medulloblastomas, translocations are also included. The published data on which this figure is based are provided in table S1D.



the majority of translocations appear to be passengers rather than drivers

B Vogelstein et al. Science 2013;339:1546-1558

Metodo para identificar y clasificar genes mutaciones en proteinas conductoras de cancer

PATRON MUTACIONAL (mas que la frecuencia)

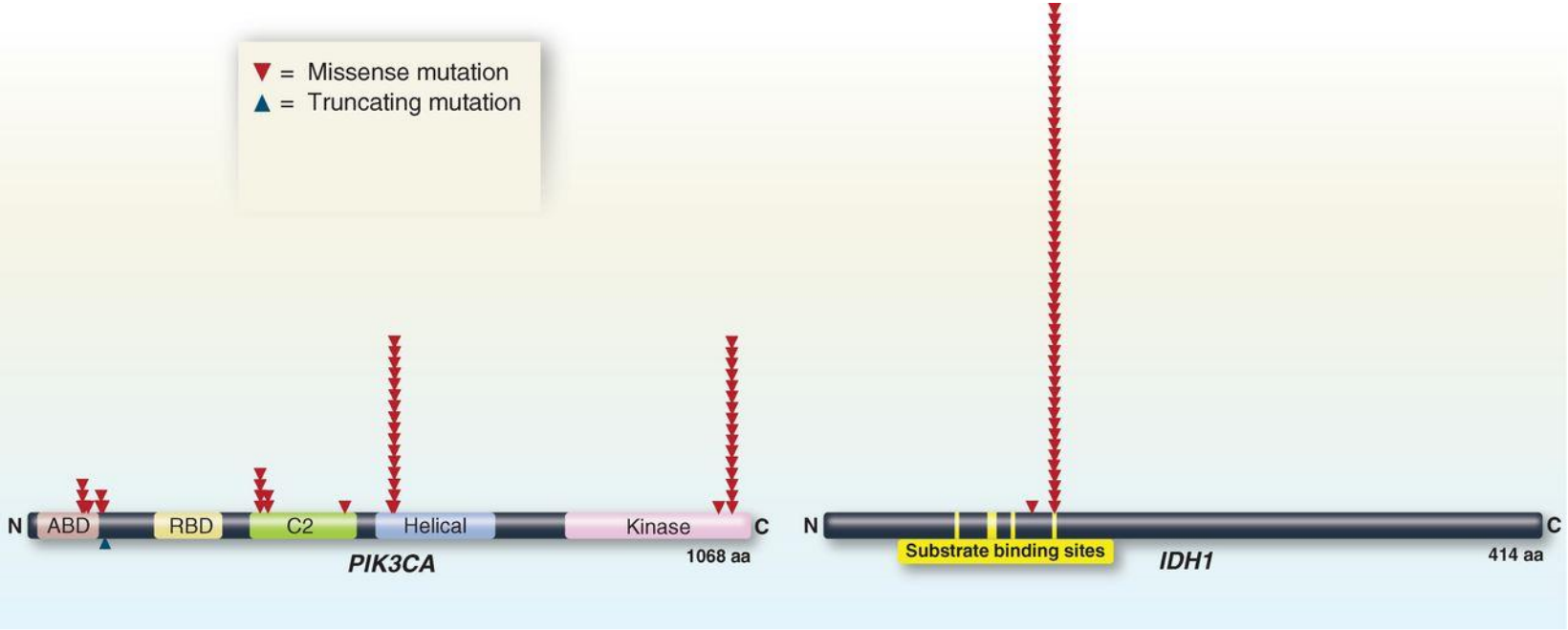


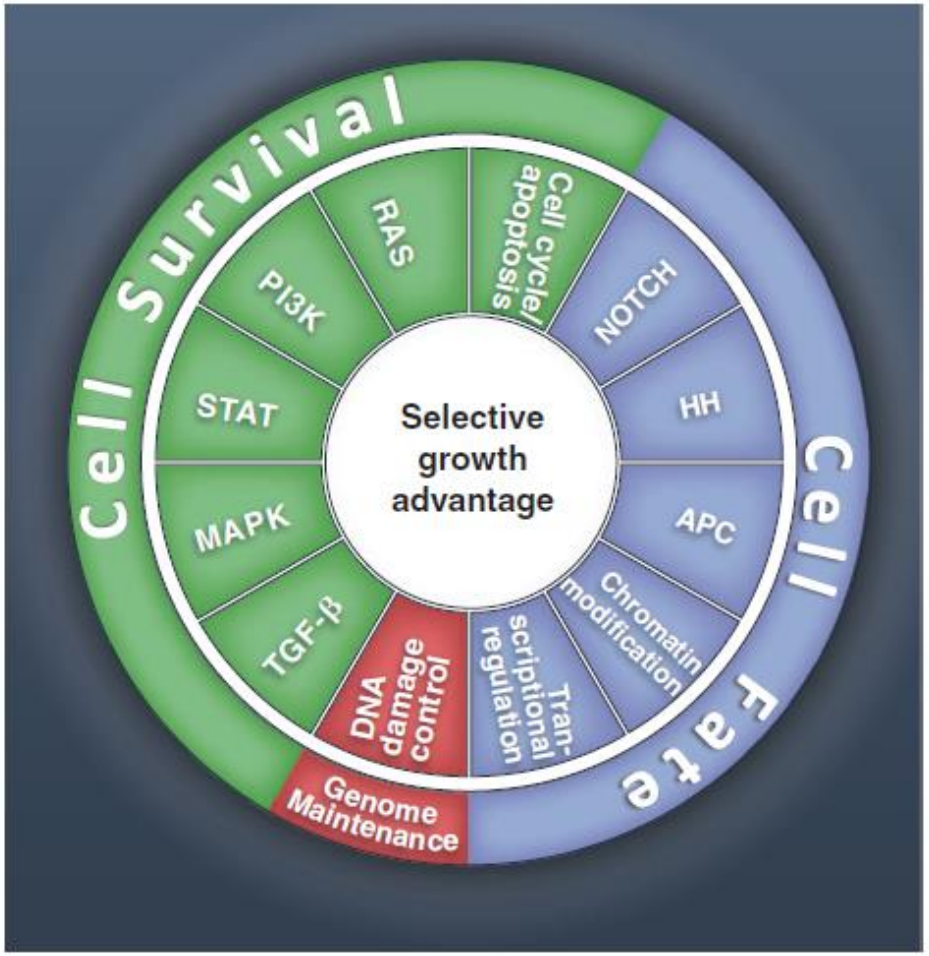
Fig. 4 Distribution of mutations in two oncogenes (PIK3CA and IDH1) and two tumor suppressor genes (RB1 and VHL).

Published by AAAS

B Vogelstein et al. Science 2013;339:1546-1558

Cancer cell signaling pathways and the cellular processes they regulate

- All of the driver genes listed in table S2 can be classified into one or more of **12 pathways** (middle ring) that confer a selective growth advantage (inner circle; see main text).
- These pathways can themselves be further organized into three core cellular processes (outer ring).



Genómica de cáncer

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- Aplicación a la medicina de precisión

P5-Mutaciones NO CODIFICANTES

- Que regiones NO CODIFICANTES conoce?

- Están mutadas en cáncer?
- Pueden ser conductoras de cáncer?

- Existen cambios en la regulación de la expresión génica que no son CODIFICANTES? Qué tipo conoce?

Classic epidemiologic studies have suggested that solid tumors ordinarily require five to eight “hits, but molecular data found less..

Mutaciones sinónimas
Regiones reguladoras
Sittios de Splicing
ncRNAs

Published online: March 18, 2016

Review

OPEN ACCESS

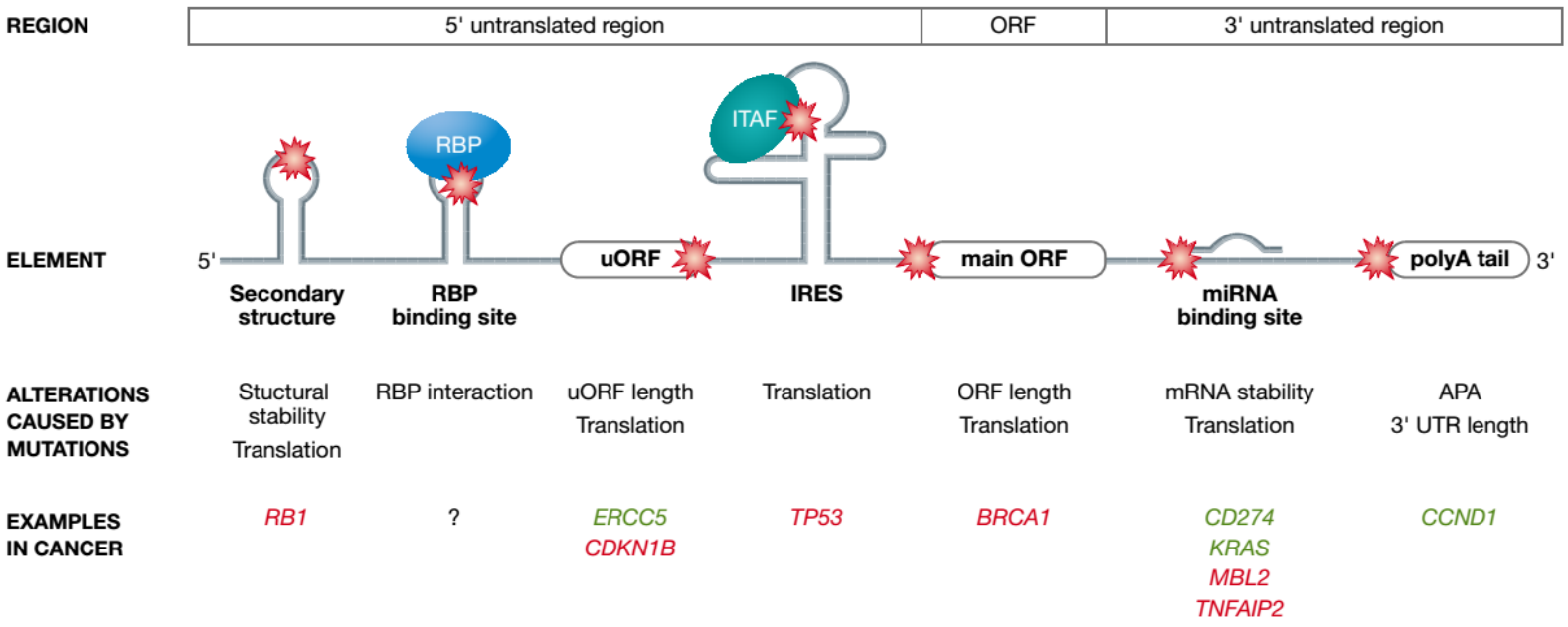
EMBO Molecular Medicine

The dark matter of the cancer genome: aberrations in regulatory elements, untranslated regions, splice sites, non-coding RNA and synonymous mutations

Sven Diederichs[1,2,3,*], Lorenz Bartsch[4,†], Julia C Berkmann[4,†], Karin Fröse[4,†], Jana Heitmann[4,†], Caroline Hoppe[4,†], Deetje Iggena[4,†], Danny Jazmati[4,†], Philipp Karschnia[4,†], Miriam Linsenmeier[4,†], Thomas Maulhardt[4,†], Lino Möhrmann[4,†], Johannes Morstein[4,†], Stella V Paffenholz[4,†], Paula Röpenack[4,†], Timo Rückert[4,†], Ludger Sandig[4,†], Maximilian Schell[4,†], Anna Steinmann[4,†], Gjendine Voss[4,†], Jacqueline Wasmuth[4,†], Maria E Weinberger[4,†] & Ramona Wullenkord[4,†]

Abstract

EMBO Mol Med (2016) 8: 442–457



ENCODE

Encyclopedia of DNA Elements

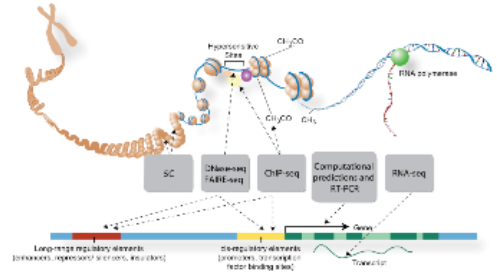
ROADMAP epigenomics PROJECT

Encyclopedia of DNA Elements

https://www.encodeproject.org/

About ENCODE Data

The Encyclopedia of DNA Elements (ENCODE) Consortium is an international collaboration of research groups funded by the National Human Genome Research Institute (NHGRI). The goal of ENCODE is to build a comprehensive parts list of functional elements in the human genome, including elements that act at the protein and RNA levels, and regulatory elements that control cells and circumstances in which a gene is active.



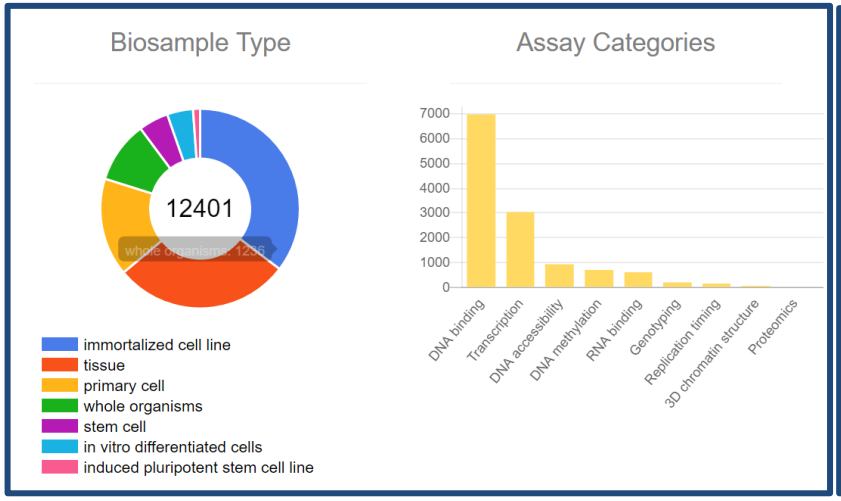
Click to enlarge

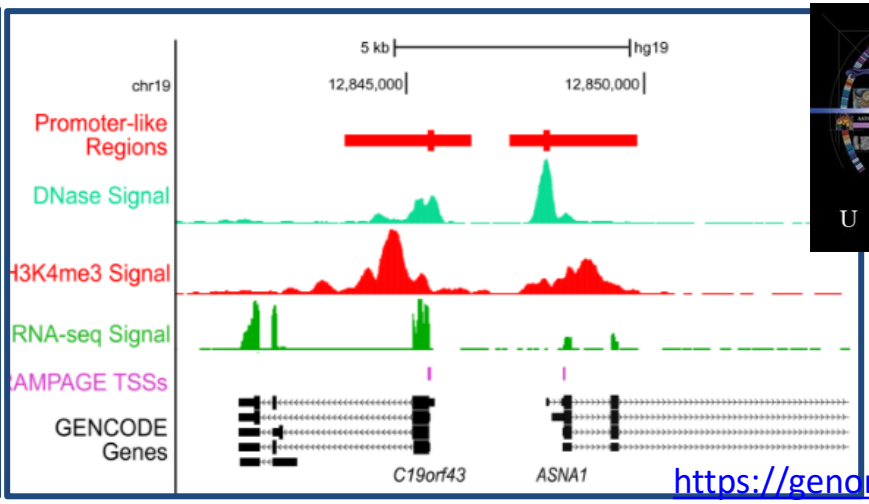
ENCODE data are now available for the entire human genome. ***All ENCODE data are free and available for immediate use via*** :

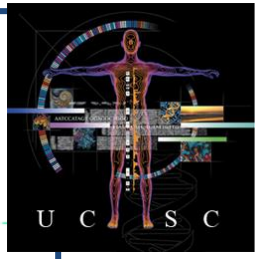
- Search for displayable tracks and downloadable files
- Download of data files
- Visualization in the UCSC Genome Browser (ENCODE data marked with the NHGRI logo)
- Data mining with the UCSC Table Browser and other UCSC Genome Bioinformatics tools

To search for ENCODE data related to your area of interest and set up a browser view, use the UCSC Experiment Matrix or Track Search tool (*Advanced* features). The Experiment List (Human) and Experiment List (Mouse) links provide comprehensive listings of ENCODE data that is released or in preparation.

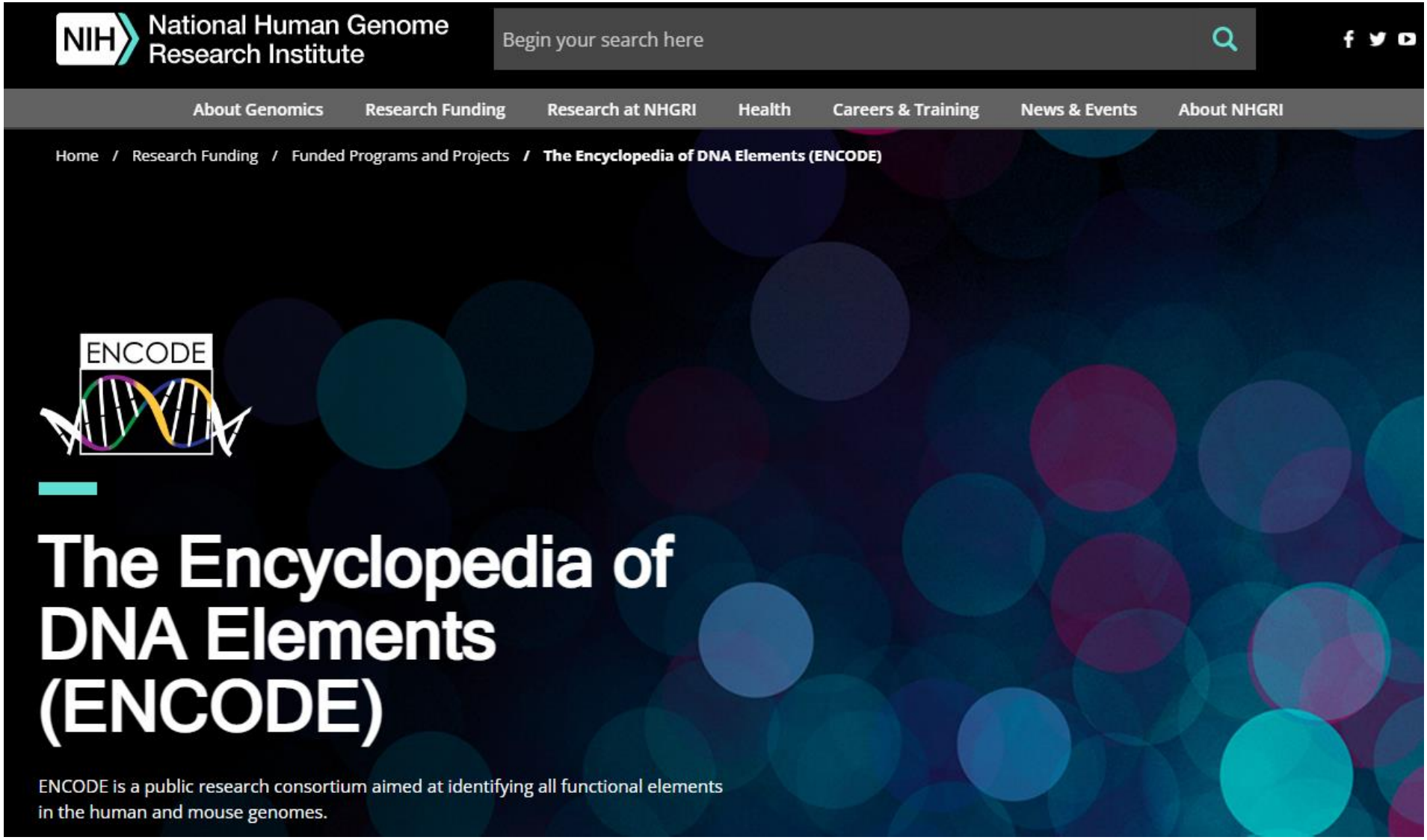
All ENCODE data is freely available for download and analysis. However, before publishing research that uses ENCODE data, please read the ENCODE Data Release Policy, which places some restrictions on publication use of data for nine months following data release. Read more about ENCODE data at UCSC.







https://genome.ucsc.edu/



ENCODE 4 seeks to expand the catalog of candidate regulatory elements in the human and mouse genomes through the study of a broader diversity of biological samples including those associated with **disease** as well as by employing novel assays not used previously in ENCODE.

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P6-APLICACIONES de la Genómica del cáncer a la medicina

- ¿Qué es la medicina de precisión?
- ¿ Qué son los fármacos dirigidos a blanco molecular?
- ¿ La genómica aporta a la medicina de precisión en cáncer? Explique.
- ¿ Qué criterios utilizaría para decidir si secuencia genoma, exoma, un grupo de genes o un gen solo de un tumor?
- ¿ Qué criterios utilizaría para decidir la fuente de ADN a secuenciar en un paciente oncológico (tejido tumoral fijado, biopsia, células circulantes, ADN circulante, orina)?
- ¿ Qué propiedades de las variantes encontradas pueden ser anotadas y ayudan a determinar su patogenicidad?

Los pilares del tratamiento del cáncer

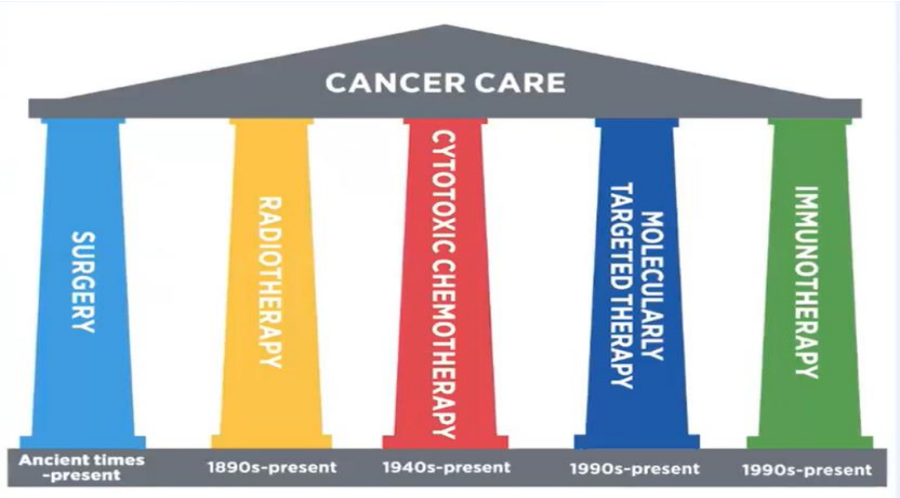
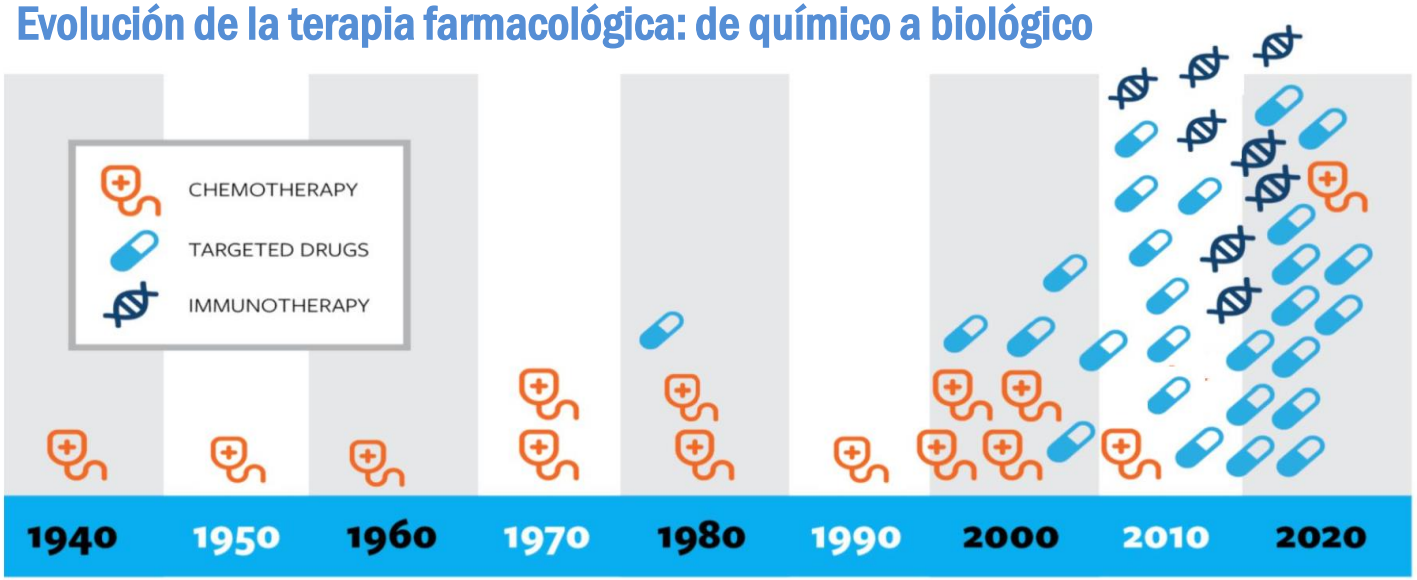


Image Credit AACR 2018 Annual Report

Evolución de la terapia farmacológica: de químico a biológico



https://www.lungcancerresearchfoundation.org/research/why-research/treatment-advances/

Genómica al servicio de la medicina de precisión en Oncología:

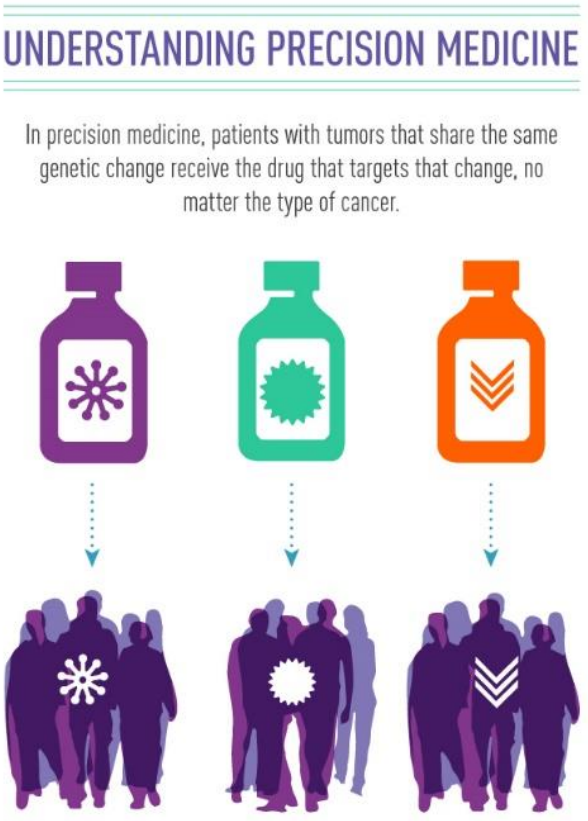
Tamiz-Biomarcadores
Diagnostico
Pronostico
Predicción: quimio, radio, biológica

Pruebas genómicas avanzadas

Advanced genomic testing (AGT)

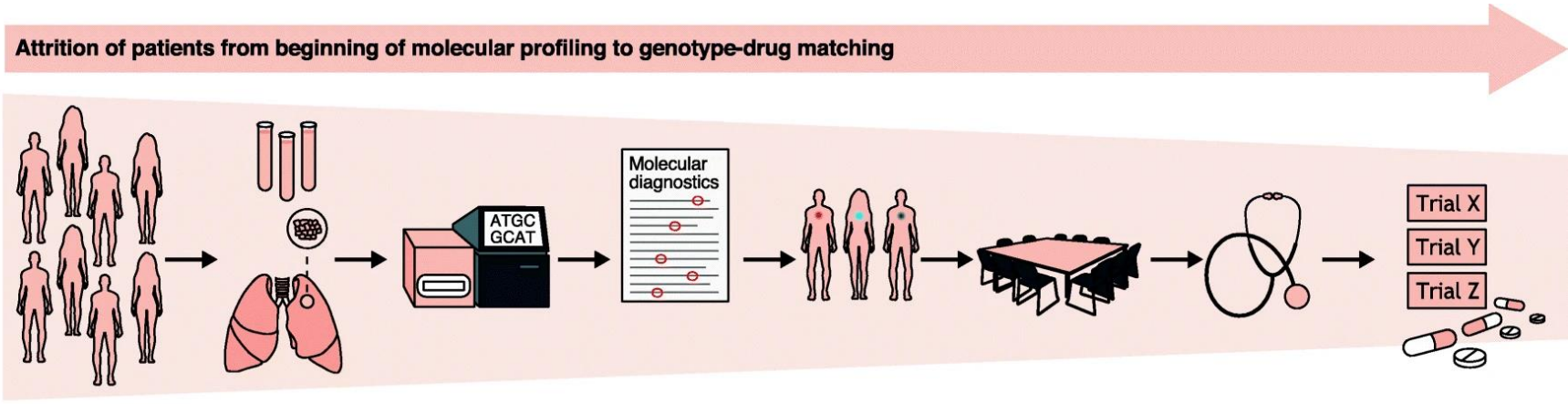
Las pruebas genómicas avanzadas están diseñadas para ayudar a identificar las alteraciones del ADN que pueden estar impulsando el crecimiento de un tumor específico. La información sobre las mutaciones genómicas que son exclusivas de su cáncer individual puede ayudar a los médicos a identificar tratamientos diseñados para atacar esas mutaciones.

Medicina de precisión



Terapias dirigidas a
Blanco molecular

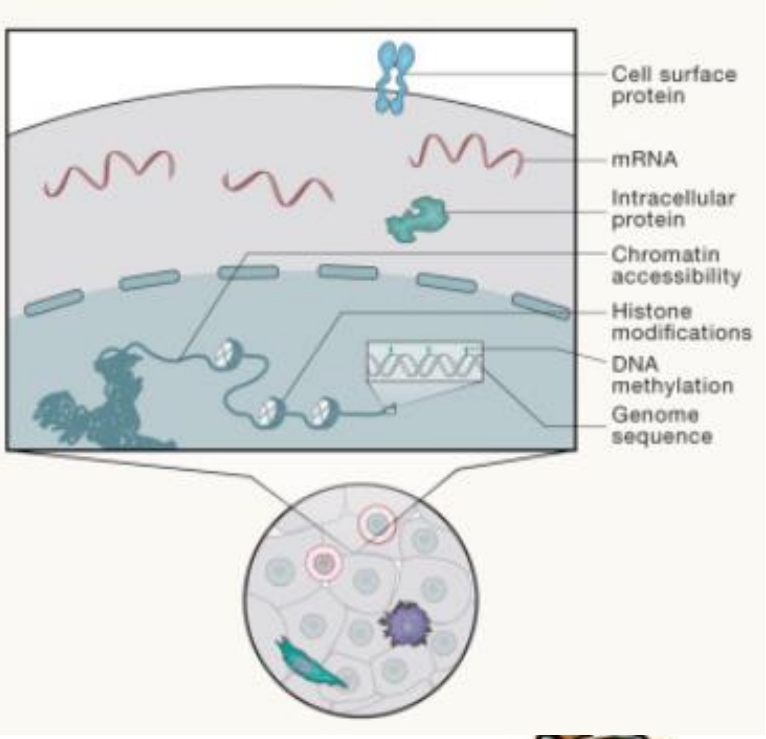
El proceso desde la secuenciación genética de los pacientes hasta la inscripción en ensayos clínicos de genotipo apareado.

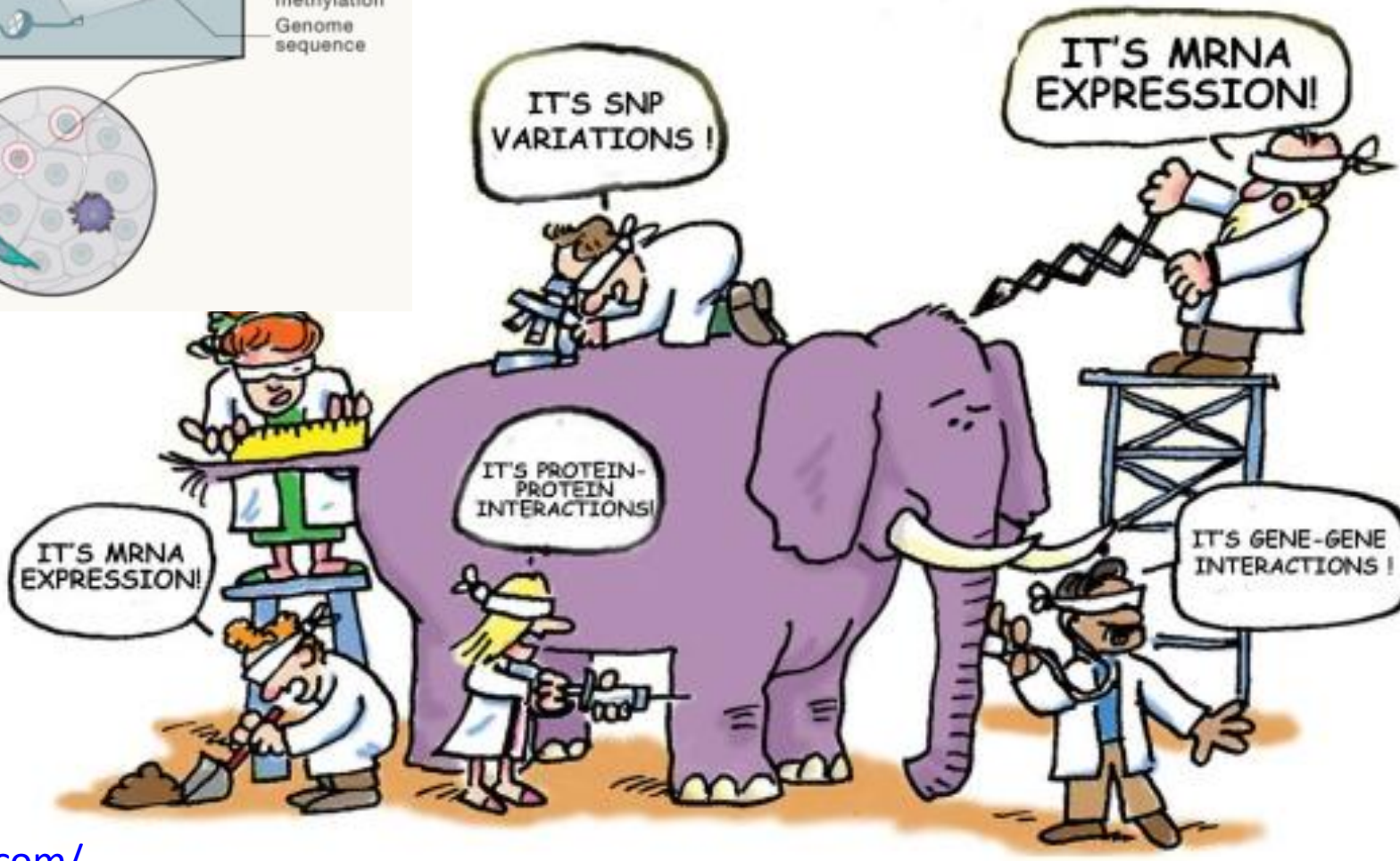


	Patient accrual	Sample collection	Laboratory operations	Variant interpretation	Clinical utility	Decision	Clinical interpretation	Trial matching
Examples of challenges	Patient factors: medical, logistics	Inadequacy of samples for profiling	Technical issues of NGS and other assays	Challenges with variant interpretation	Low rate of actionable results	Lack of access to MTB	Physician factors: busy clinics, lack of genomic understanding	Lack of access to drugs or clinical trials
Possible solutions	Appropriate patient selection, navigators, efficient consent and IRB aprocesses	Improvement in sample collection and processing, liquid biopsies	Advances in technology including limits of detection and coverage depth	Integrated knowledge bases, artificial intelligence tools for automation	Expansion of target identification beyond genomics	Increase availability to MTB e.g. virtual MTB	Navigators and tools to help physicians manage profiling results	Increase number and access to precision medicine trials; easier access to approved drugs

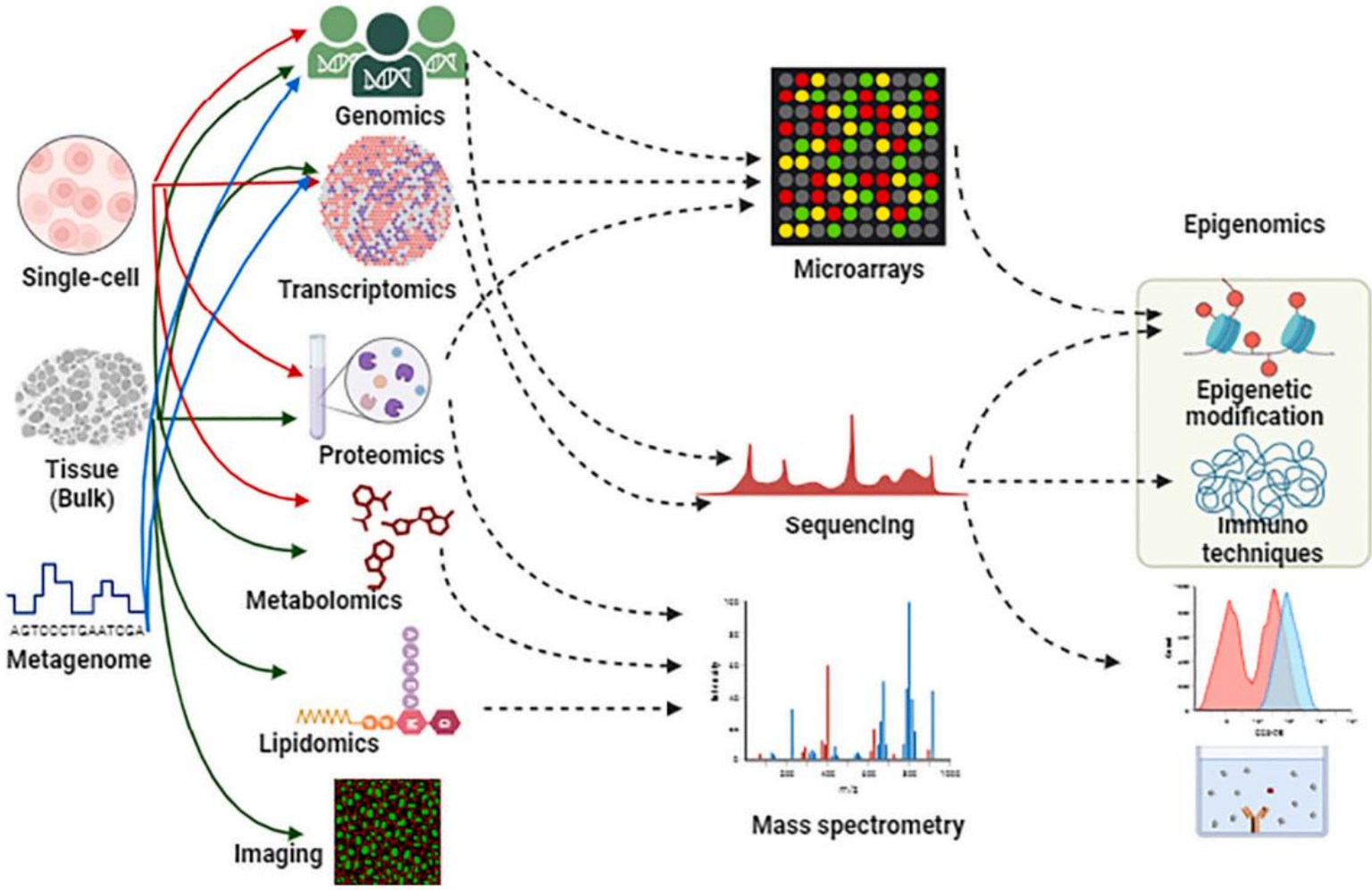
MTB, placa de tumores moleculares;
IRB, junta de revisión institucional;
NGS, secuenciación de próxima generación

Genome Medicine volume 12, Article number: 8 (2020)

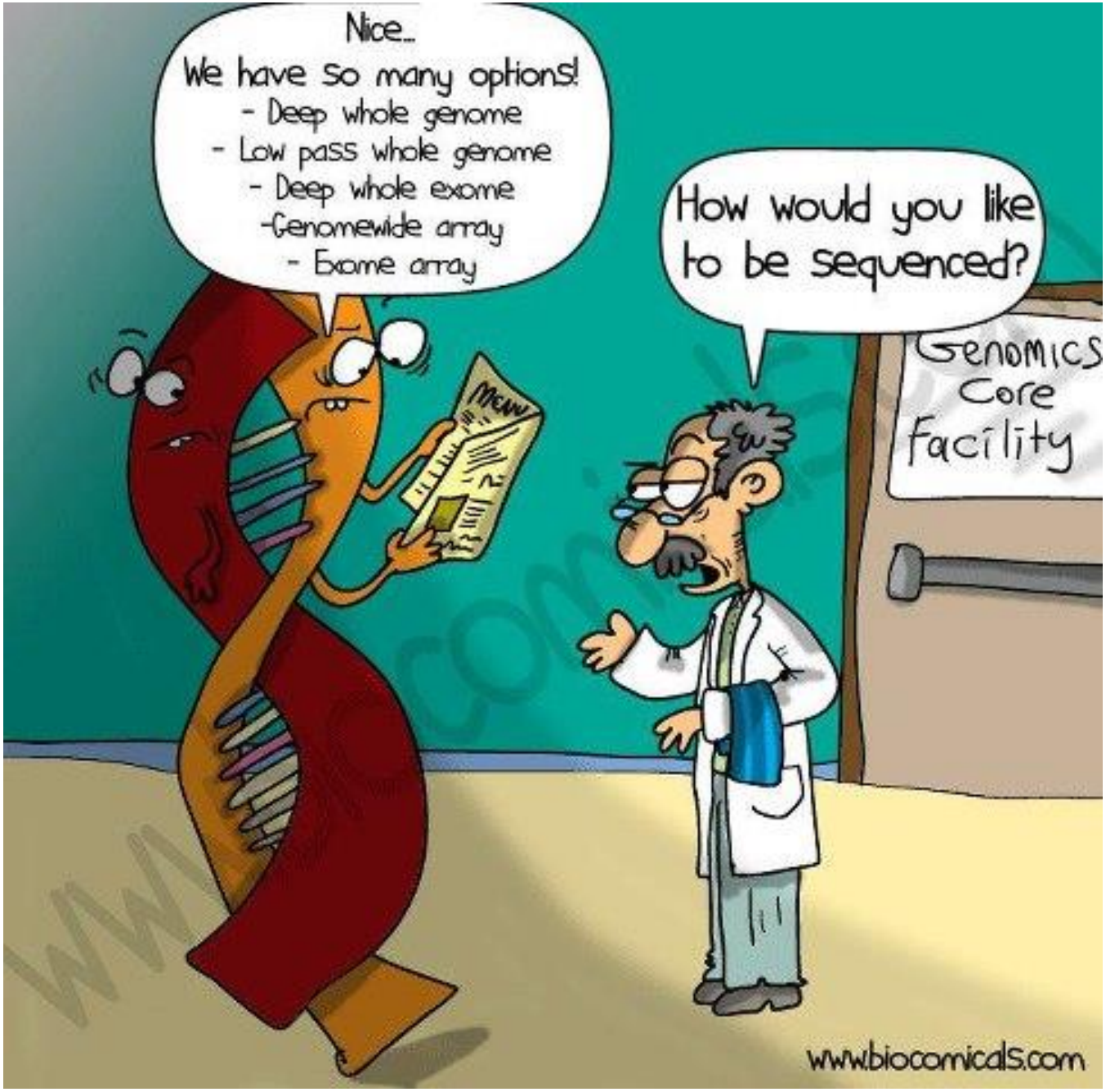


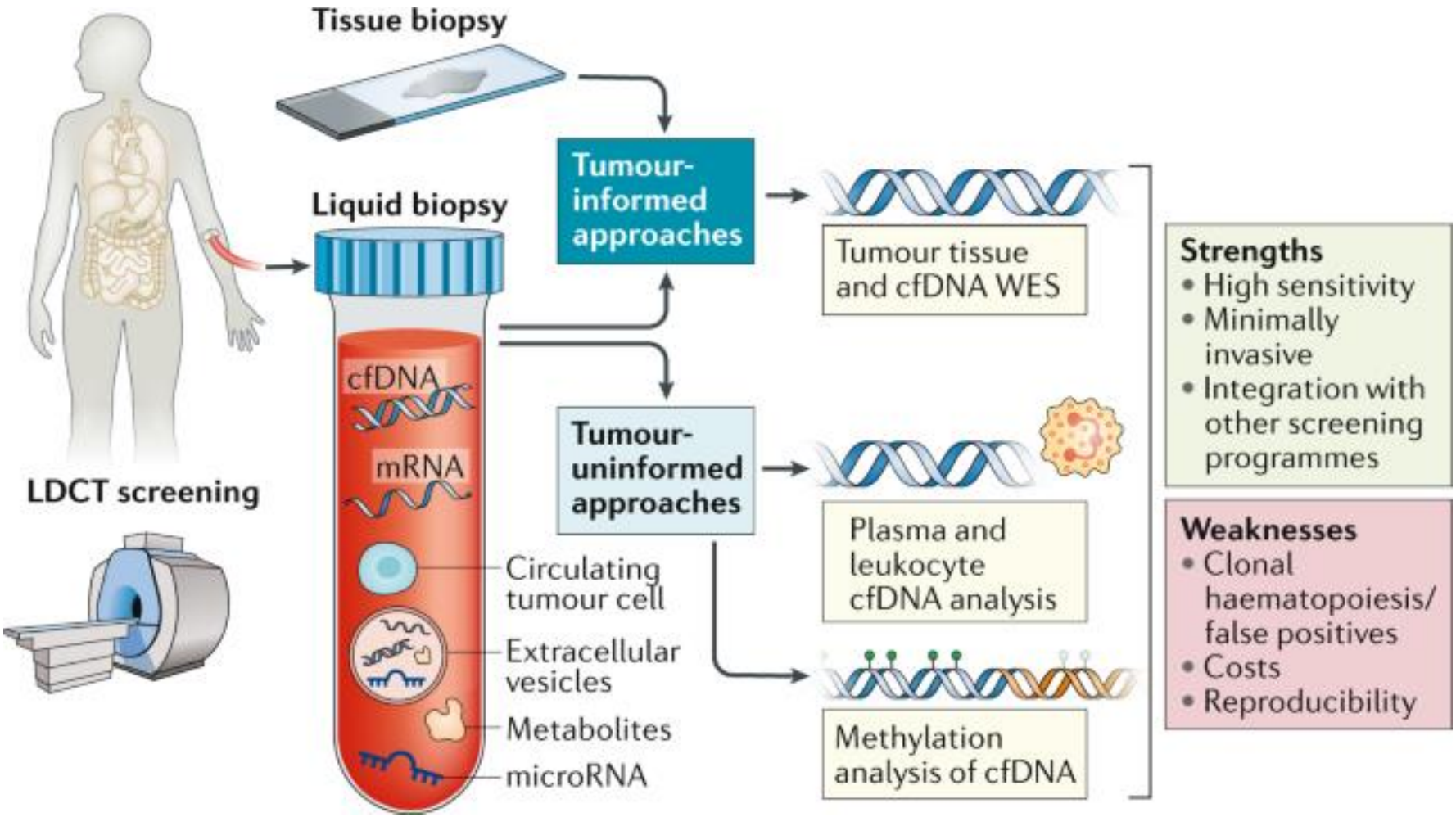


https://accelom.com/



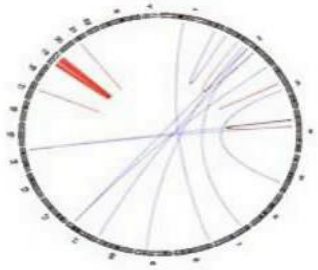
Multi-OMICS approaches in cancer biology: New era in cancer therapy
Sohini Chakraborty et al 2024.


Nice...
We have so many options!
- Deep whole genome
- Low pass whole genome
- Deep whole exome
-Genomewide array
- Exome array
How would you like to be sequenced?
Genomics Core Facility
www.biocomicals.com


Tissue biopsy
Liquid biopsy
LDCT screening
cfDNA
mRNA
Circulating tumour cell
Extracellular vesicles
Metabolites
microRNA
Tumour-informed approaches
Tumour-uninformed approaches
Tumour tissue and cfDNA WES
Plasma and leukocyte cfDNA analysis
Methylation analysis of cfDNA
Strengths
• High sensitivity
• Minimally invasive
• Integration with other screening programmes
Weaknesses
• Clonal haematopoiesis/ false positives
• Costs
• Reproducibility

Whole-genome sequencing

All genes, translocations and non-coding DNA

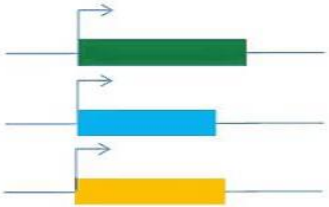


Lower coverage

Slower (several weeks), all mutations tested but lower accuracy

Whole-exome sequencing

22,000 genes



Intermediate coverage

Slower (a few weeks), good accuracy, many mutations tested

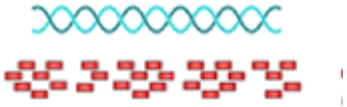
Targeted panel sequencing

40-400 genes

High coverage

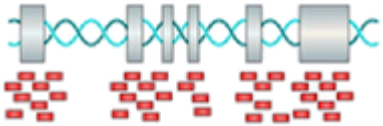
Rapid (a few days), high accuracy but small number of mutations tested

Whole genome sequencing



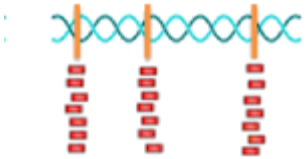
- Sequencing region : whole genome
- Sequencing Depth: >30X
- Covers everything – can identify all kinds of variants including SNPs, INDELs and SV.

Whole exome sequencing



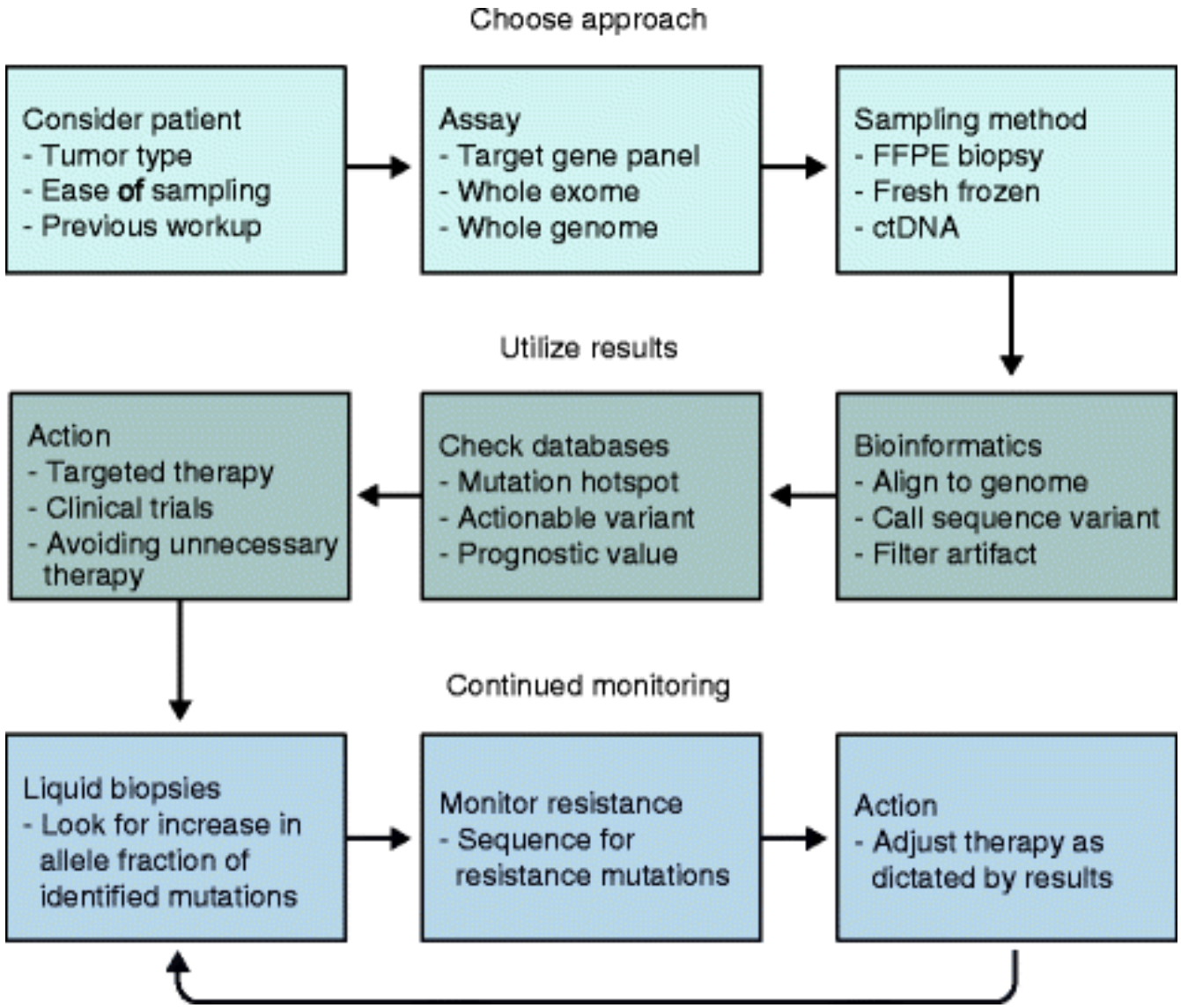
- Sequencing region: whole exome
- Sequencing Depth : >50X ~ 100X
- Identify all kinds of variants including SNPs, INDELs and SV in coding region.
- Cost effective

Targeted sequencing



- Sequencing region: specific regions (could be customized)
- Sequencing Depth : >500X
- Identify all kinds of variants including SNPs, INDELs in specific regions
- Most Cost effective

El diagrama de flujo de la Medicina de Precisión



https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-015-0203-x

Variant classification by the Joint Consensus Recommendation (JCR) and by the Harmonized Evidence Levels (HEL).

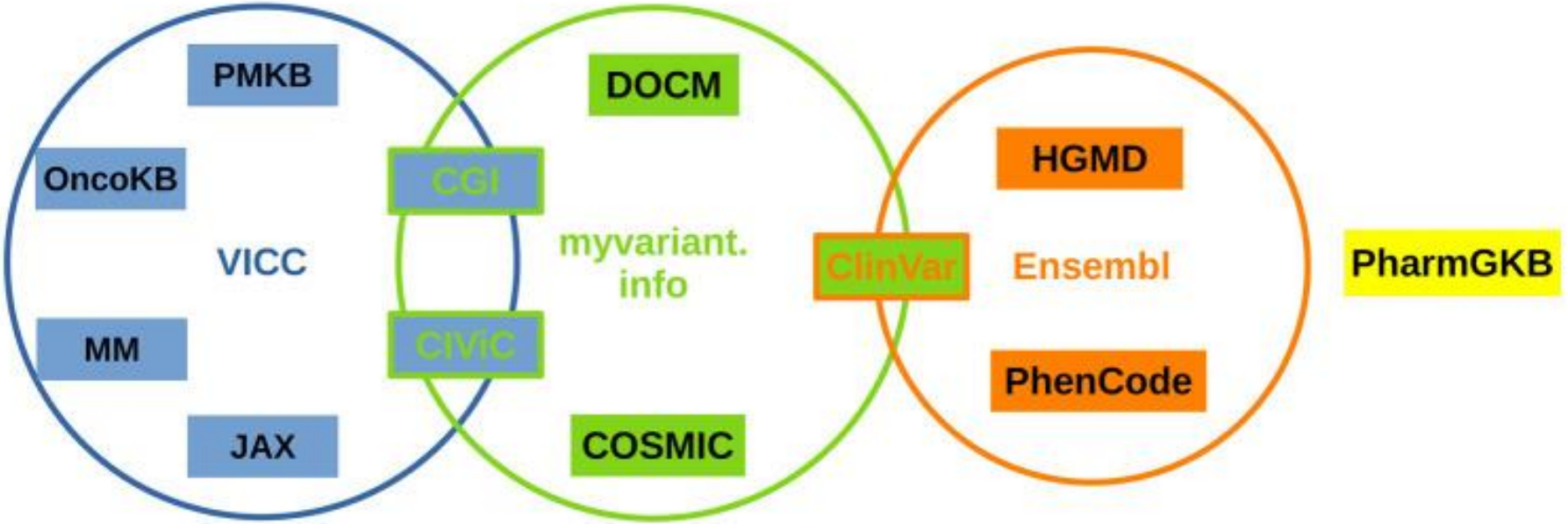
These classifications distinguish between variants with clinical actionability (tier I and II, graded by evidence level A-D), variants of unknown clinical significance (tier III) and benign variants (tier IV).

Table I. *Variant classification by the Joint Consensus Recommendation (JCR) and by the Harmonized Evidence Levels (HEL). These classifications distinguish between variants with clinical actionability (tier I and II, graded by evidence level A-D), variants of unknown clinical significance (tier III) and benign variants (tier IV).*

Category by JCR	Definition	Category by HEL	Definition
Tier I	Variants with strong clinical significance	Level A	Evidence from professional guidelines or Food and Drug Administration-approved therapies relating to a biomarker and disease.
		Level B	Evidence from clinical trials or other well-powered studies in clinical populations, with expert consensus.
Tier II	Variants with potential clinical significance	Level C	Evidence for therapeutic predictive markers from case studies, or other biomarkers from several small studies. Also, evidence for biomarker therapeutic predictions for established drugs for different indications.
		Level D	Preclinical findings or case studies of prognostic or diagnostic biomarkers. Also includes indirect findings.
Tier III	Variants of unknown clinical significance		
Tier IV	Benign/likely benign variants		

The Global Alliance for Genomics and Health's **Variant Interpretation for Cancer Consortium** (**VICC)** has published standards for genomic data sharing and provided and a classification system called Harmonized Evidence Level

Bases de datos para interpretar si los cambios (variantes) en el ADN tumoral identificados por secuenciación tiene utilidad clínica: INTERPRETACION de "VARIANTES GENICAS"



Meta-databases are presented as circles, individual databases as rectangles. The intersection between the circles represents databases which are available within several meta-databases.
CGI: Cancer Genome Interpreter's variants database; CIViC: Clinical Interpretations of Variants in Cancer; ClinVar: Clinical Variants of the National Center for Biotechnology Information; COSMIC: Catalogue of Somatic Mutations in Cancer; DOCM: Database of Curated Mutation; HGMD: Human Gene Mutation Database; JAX: Jackson Laboratory Clinical Knowledgebase; MM: MolecularMatch; OncoKB: Oncology Knowledge Base; PharmGKB: Pharmacogenomics Knowledgebase; PhenCode: Phenotype for ENCODE; PMKB: Precision Medicine Knowledgebase; VICC: meta-database of the Variant Interpretation for Cancer Consortium.

Conclusion of Banck H et al 2021 (MDS/AML): A single public variant database is currently not sufficient to interpret clinical variant. meta-database show a promising development. Manual interpretation of variants by experts and tumor boards remains obligatory.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7943210/

Gracias!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